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Title page

Title

A systematic review and meta-analysis of prognostic factors of acute exacerbation of idiopathic pulmonary fibrosis

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Abstract

Objective

To clarify prognostic factors of acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF).

Design

A systematic review and meta-analysis.

Data sources

Medline, EMBASE and Science Citation Index Expanded were searched from 2002 through 1 March 2019.

Eligibility criteria for selecting studies

The review included primary studies addressing the association between the outcomes such as all-cause mortality of AE of IPF and its potential prognostic factors, which were designated as any clinical information related to the outcomes.

Data extraction and synthesis

Two reviewers extracted relevant data independently and assessed risk of bias. Univariate results were pooled using a random-effects model if at least three studies were available. Prognostic factors were determined based on significant and consistent results on both univariate and multivariate analyses in the majority of studies.

Results

Out of a total of 6763 articles retrieved, 37 were eligible and cumulatively, 30 potential prognostic factors for all-cause mortality were selected. Each study was subject to certain methodological shortcomings. The following five factors were statistically significant by a meta-analysis of univariate results, which was confirmed by multivariate analysis, i.e., Acute Physiology and Chronic Health Evaluation (APACHE) II score (hazard ratio (HR) 1.09, 1.04-1.15), partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio (HR 0.95, 0.92-0.97/odds ratio (OR) 0.92, 0.89-0.95), lactate dehydrogenase (LDH) (HR 1.02, 1.01-1.02/standardized mean difference (SMD) 0.48, 0.11-0.84), white blood cell (WBC) count (MD 1.35, 0.19-2.51) and oxygen therapy before AE (HR 1.88, 1.15-3.09) (pooled estimates of univariate

results, 95% confidence interval). The quality of the presented evidence was rated as either low or very low.

Conclusions

APACHE II score, PaO2/FiO2 ratio, LDH, WBC count and oxygen therapy before AE were deemed as prognostic factors of AE of IPF. However, the findings should be interpreted cautiously due to the low evidence level.

Registration

CRD 42018106172

Keywords

Idiopathic pulmonary fibrosis, acute exacerbation, prognosis, systematic review, meta-analysis

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis addressed the shortcoming in previous reports of prognostic factors of AE of IPF, which were composed of only small studies and thus may have generated spurious results.
- All primary studies were subject to certain methodological constraints, which undermined the quality of evidence derived from this review.
- An applicability of the findings may be limited because most of the reports constituting this review were derived from only one region.

Introduction

Interstitial pneumonia (IP) is a heterogeneous clinical entity, which is characterized by common pathological findings of fibrosis in the interstitium of pulmonary parenchyma.[1] Idiopathic pulmonary fibrosis (IPF) is the most common IP among idiopathic IPs (IIPs) with no apparent causes.[2] The disease has been at the centre of vigorous research over the last few decades given the evolution of diagnostic modalities.[3] IPF is known to be a fatal disease leading to respiratory failure due to its natural progression [4] and other comorbidities such as lung cancer, infection and cardiovascular diseases.[5] However, the most common cause of deaths of IPF is the event called an acute exacerbation (AE), occurring in approximately 40% of the cases.[6] This unique phenomenon was first reported as small case series, in which three patients with IPF presented with acute worsening of respiratory symptoms alongside with newly emerging bilateral radiological opacities that were related to no identifiable causes.[7] Subsequently, AE of IPF was recognized as not uncommon phenomenon and defined both clinically and radiologically by the latest international diagnostic criteria.[8] The pathogenesis of AE of IPF is still unknown although previous research disputed whether it is an autonomic acceleration of fibrotic process or an aggravation caused by external stimuli.[9] It is unpredictable in most cases regardless of some risk factors described by previous studies.[10] Once AE of IPF develops, the prognosis of this condition is extremely dismal due to no established therapeutic options.[11] However, there is a variation of mortality in previous reports, e.g., an estimated in-hospital mortality of 80% by an earlier study [12] and 90-day mortality of 70% by a recent study.[13] These discrepancies may suggest that the prognosis of AE of IPF varies between patients although between-study variations may be largely attributed to selection bias.[14] The knowledge of prognostic factors that would determine the prognosis of an individual patient is vital to make a therapeutic strategy, provide patients and families with relevant information to guide their decision-making and help design future research of pharmaceutical intervention.[15] Some research groups previously investigated prognostic factors of AE of IPF.[16] However, these previous findings may be anecdotal because most of them were derived from retrospective studies with a small sample size.[17] In addition, a prospective cohort study to investigate prognostic factors of AE of IPF may be unfeasible because of the unpredictable course of the disease, preventing recruitment of a larger sample size.[18] Therefore, the aim of this systematic review and meta-analysis was to overcome the limitation of a primary study in this research area and summarize current evidence

regarding prognostic factors of AE of IPF. This study was registered with International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018106172).

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[20] The methods were described briefly as the in-depths of methodology of this study were reported as a protocol paper beforehand.[21]

Patient and public involvement

There was no patient and public involvement in the whole process of conducting this research.

Eligibility criteria

Patients with AE of IPF were eligible for this review. AE and IPF were diagnosed based on previously published international guidelines relevant to respective condition or disease.[22-23] Subjects who presented with rapidly progressive IP at the first visit was included if radiological and/or pathological usual interstitial pneumonia (UIP) with no identifiable causes was confirmed. Only the first episode of AE was eligible if it was repeatedly manifested. The primary outcomes were short-term all-cause mortality and pulmonary-cause mortality, which were defined as in-hospital or 30-day mortality. The secondary outcomes were the proportion of patients discharged from the hospital and long-term all-cause mortality, which was determined at 90 days (3 months), 180 days (6 months) or 1 year after the diagnosis of the disease. Long-term health-related quality of life (hQOL) was also considered as the secondary outcome. All primary study types excluding case reports were considered for the review if quantitative data was available for any clinical information that had been investigated for their association with the outcomes. Editorials, letters, review articles and conference proceedings were not considered. Only research papers published in English in 2002 or later were reviewed as 2002 marked the year when the current classification system of IIPs was first introduced.[24]

Search strategy

Electronic databases, i.e., Medline (Ovid), EMBASE (Ovid) and Science Citation Index Expanded (Web of Science) were searched using subject headings and text words related to study population such as 'idiopathic pulmonary fibrosis' and 'acute exacerbation' (e-Appendix). The search was conducted on the 1st of March 2019. The reference lists of eligible studies and relevant review articles were also hand-searched to find additional reports. Grey literature was identified using Google Scholar.[25]

Study selection and data extraction

Two reviewers (H.K. and O.M.P.) independently examined the titles and abstracts of all retrieved articles to identify eligible reports. Data was extracted based on a modified data extraction form, which was previously published in a protocol paper reviewing prognostic factors.[26] Extracted data included first author's name, year of publication, study location, study design, sample size and their demographic features, outcomes, potential prognostic factors and their effect estimates, methods for statistical analysis and items associated with risk of bias. Any uncertainties or disagreements between reviewers arising from these processes were resolved through discussions. Authors were contacted to inquire about uncertain data or request for additional relevant information.

Potential prognostic factors

Any clinical information relevant to the pre-defined outcomes, which was reported by a minimum of three separate studies using either univariate or multivariate analysis, was further investigated as potential prognostic factors for this review. If the same research group reported a certain potential prognostic factor for a certain outcome in multiple studies, only the result derived from the study with the largest sample size was considered.

Risk of bias in individual studies

The Quality in Prognostic Studies (QUIPS) tool was applied to assess risk of bias in individual studies. Overall risk of bias was rated as previously reported.[27]

Statistical analysis

Summary statistics and statistical synthesis

The effect of potential prognostic factors was summarized with hazard ratios (HRs), odds ratios (ORs) or mean difference (MD) depending on the types of available data. If an association between a potential prognostic factor and an outcome of interest was presented using the same summary statistics in three or more studies, the results were

statistically combined. Pooled results were summarized separately using HRs, ORs or MD. If the unit of MD varied between studies, standardized MD (SMD) was calculated for meta-analysis.[28] Only unadjusted effect estimates of potential prognostic factors were combined and the effect estimates derived from multivariate models were described qualitatively. If meta-analysis was feasible from the collated data, it was conducted using a random-effects model employing the DerSimonian and Laird method.[29] Meta-analysis was conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All the results were presented with the 95% confidence interval (CI) if available and the 95% prediction interval (PI) was also calculated if the effect estimates were pooled and there was heterogeneity between studies.[30] Statistical significance was considered with a p-value of <0.05. If combining data was deemed inappropriate (due to a small number of studies or substantial clinical or methodological variability between studies), the results were reported qualitatively.

Heterogeneity

Between-study variance was estimated using the Tau^2 value and assessed using both Q statistic and I^2 value. For the assessment of heterogeneity between studies, statistical significance was considered with a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity was categorised as mild (0 to 30%), moderate (30 to 50%), considerable (50 to 70%) and substantial (70 to 100%).[31] To better interpret sources of heterogeneity, a subgroup analysis was to be conducted based on the definition of AE of IPF (idiopathic or triggered),[8] study location (Asia or non-Asia) and sample sizes ($N \leq 50$ or $N > 50$) if there was statistically significant heterogeneity. As mortality was defined at a varied point in time by an individual study, it was also considered in subgroup analysis. Sensitivity analysis was to be conducted focusing on studies with low risk of bias.

Small study bias

Small study bias such as publication bias was to be examined using graphical asymmetry of a funnel plot and the Egger's test,[32] if 10 or more studies were available for meta-analysis. A p-value of <0.1 was considered as statistical significance due to the low power of the test. If publication bias was suspected, an adjusted summary effect was to be estimated using the trim and fill method.[33]

Confirmation of prognostic factors

Prognostic factors were confirmed if their effects were in the same direction and statistically significant in the majority of studies by both univariate and multivariate analyses. If a meta-analysis was conducted, its pooled effect was assigned to each study constituting the analysis in estimating the significance and consistency of individual studies. In other words, the effect estimate of individual studies was overridden by the result of meta-analysis to calculate the number of significant and consistent studies.

Confidence in cumulative evidence

The credibility of evidence generated from this systematic review was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.[34] The GRADE system was applied to the final list of confirmed prognostic factors generated from both univariate and multivariate results.

Results

Search strategy

A total of 6763 reports were identified through Medline, EMBASE, Science Citation Index Expanded and Google Scholar. After excluding 1368 duplicates, 79 non-English records, 3293 reports of ineligible study types (consisting of 1353 conference proceedings, 1068 review articles, 294 editorials or letters and 578 case reports) and 1917 articles that did not relate to the topic of interest, the remaining 106 reports were obtained as full-texts. Out of these, 69 reports were excluded due to no prognosis in 43 studies, IP other than IPF in 12 studies, deterioration other than acute exacerbation in 3 studies, an inclusion of stable IPF in 5 studies, multiple episodes of AE in one study and no quantitative data in 5 studies. Finally, 37 articles/studies [35-71] were eligible for this review (e-Figure 1, e-Table 1). No additional reports were identified from other potential sources.

Overview of included studies and potential prognostic factors

A total of 34 studies were conducted in Asia. Out of them the majority of studies took place in Japan (n=27), followed by Korea (n=6) and China (n=1). Two of the remaining 3 studies were conducted in Italy and the other one was in Greece. Twenty-three studies and one study utilized a retrospective and a prospective cohort study design,

respectively, and the rest used a case-control design. Twenty-four studies had a sample size of ≤50 participants and the other 13 studies had 51 to 100 participants, which yielded a total number of 1607 patients included in this review. The outcomes were all-cause mortality in 35 studies and disease-related mortality in 2 studies. The measure of hQOL was also described in one study. A total of 8 research groups conducted multiple studies using the same cohort and published reports (Collard 2010,[40] Kim 2006,[50] Lee 2012 [54] and Song 2011[62]; Kishaba 2018 [51] and Kishaba 2014 [52]; Enomoto 2015,[41] Enomoto 2018 [42] and Enomoto2019 [43]; Furuya 2017,[45] Isshiki 2015,[46] Koyama 2017 [53] and Sakamoto 2018 [59]; Nikaido 2018 [55] and Sand 2018 [60]; Kataoka 2015,[48] Suzuki 2018 [64] and Yokoyama 2010 [71]; Abe 2012 [35] and Atsumi 2018 [38]; Tomioka 2007 [66] and Yamazoe 2018 [70]) (e-Table 1). Among these multiple research conducted by the same groups the study with the largest sample size was prioritized and a total of 30 potential prognostic factors, which were investigated for their association with all-cause mortality, were identified and followed by further analysis (e-Table 2).

Risk of bias

The rate of attrition was not explicitly stated and this could have biased the results in most of the cohort studies. There was also high risk of bias regarding confounding, statistical analysis and reporting in most of the studies. This was determined on the ground that many potential confounders were not addressed or insufficient detail was provided to describe the models used for the analysis. Consequently, all studies were rated as being subject to some methodological flaws (e-Table 3).

Statistical analysis

Confirmation of prognostic factors

All potential prognostic factors were reported using univariate analysis in three or more studies. Meta-analysis was conducted for 17 out of the total of 30 potential prognostic factors. The effect estimates of the following 6 factors were in the same direction and statistically significant in the majority of the studies by univariate analysis. These prognostic factors were as follows; Acute Physiology and Chronic Health Evaluation (APACHE) II score, partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio, C-reactive protein (CRP), lactate dehydrogenase (LDH), white blood cell (WBC) and oxygen therapy before AE (e-Table 4). Out of the total of 30

potential prognostic factors, 20 were reported by multivariate analysis, mostly derived from only one or two studies. Among them, the effect estimates for 10 factors were in the same direction and statistically significant in the majority of the studies. These prognostic factors were as follows; APACHE II score, distribution pattern of newly emerging radiological opacities and extent of abnormality on high resolution computed tomography (HRCT) scan, PaO2/FiO2 ratio, LDH, Krebs von den Lungen-6 (KL-6), WBC, D-dimer, neutrophil in bronchoalveolar fluid (BAL), oxygen therapy before AE (e-Table 5). Based on the criteria of prognostic factors that considered both univariate and multivariate analyses, 5 factors were confirmed as prognostic factors. The results of the other non-prognostic factors were described in a supplementary file (e-Table 4-5, e-Figure 2-20).

Effect of prognostic factors

A total of four studies reported APACHE II score using univariate analysis and the results of three studies were combined. Based on the combined result, APACHE II score was significantly associated with all-cause mortality of AE of IPF with an HR of 1.09 (95%CI: 1.04-1.15) (Figure 1). The remaining one study excluded from meta-analysis demonstrated a higher APACHE II score for non-survivors although it was not statistically significant (MD 2.80 (95%CI: -1.19-6.79) (Nikaido 2018 [55]) (e-Table 4). A multivariate analysis reported by one study demonstrated a significant result with an HR of 1.10 (95%CI: 1.10-1.19) (Kawamura 2017 [49]) (e-Table 5).

A total of 15 studies reported PaO2/FiO2 ratio using univariate analysis. The results of six studies were combined using an HR while those of other three and four studies were combined using an OR and MD, respectively. Based on the combined results, PaO2/FiO2 ratio was significantly associated with all-cause mortality of AE of IPF with an HR of 0.95 (95%CI: 0.92-0.97) (Figure 2) and an OR of 0.92 (95%CI: 0.89-0.95) (Figure 3). Another result of meta-analysis demonstrated a marginal significance with an MD of -76.3 (95%CI: -153.9-1.28) (Figure 4). Of the remaining two studies excluded from meta-analysis, one study reported a non-significant lower PaO2/FiO2 ratio for non-survivors than survivors (195 vs. 240) (Novelli 2016 [56]) whereas the other study demonstrated a point estimate in the opposite direction from the other studies with no statistical significance (HR 1.45 (95%CI: 0.71-3.03)) (Sokai 2017 [62]) (e-Table 4). A total of five studies reported PaO2/FiO2 ratio using multivariate analysis. PaO2/FiO2 ratio was demonstrated to be significantly associated with all-cause mortality in four

studies with ORs of 0.99 (95%CI: 0.98-1.00) (Kang 2018 [47]) and 0.99 (95%CI: 0.99-1.00) (Sakamoto 2018 [59]) and HRs of 0.99 (95%CI: 0.99-1.00) (Kishaba 2018 [51]) and 0.31 (95%CI: 0.14-0.67) (Suzuki 2018 [64]), respectively. In another study, the effect estimate was null value with no statistical significance (Yamazoe 2018 [70]) (e-Table 5).

A total of 13 studies reported LDH using univariate analysis. The results of seven studies were combined using an HR while those of other four studies were combined using an SMD. Based on the combined results, LDH was significantly associated with all-cause mortality of AE of IPF with an HR of 1.02 (95%CI: 1.01-1.02) (Figure 5) and an SMD of 0.48 (0.11-0.84) (Figure 6), respectively. The remaining two studies excluded from meta-analysis demonstrated similar non-significant results with ORs of 1.02 (95%CI: 1.00-1.04) (Kang 2018 [47]) and 1.01 (95%CI: 1.00-1.01) (Sakamoto 2018 [59]), respectively (e-Table 4). A total of four studies reported LDH using multivariate analysis. LDH was demonstrated to be significantly associated with all-cause mortality in three studies with HRs of 1.002 (95%CI: 1.000-1.004) (Akira 2008 [36]), 1.003 (95%CI: 1.001-1.005) (Kishaba 2018 [51]) and 1.01 (95%CI: 1.00-1.01) (Enomoto 2018 [42]), respectively. The other one study demonstrated non-significant result with an OR of 1.00 (95%CI: 1.00-1.00)) (Kang 2018 [47]) (e-Table 5).

A total of 10 studies reported WBC using univariate analysis and the results of six studies were combined. Based on the combined result, non-survivors demonstrated a significantly higher value of WBC than survivors with an MD of 1.35 (95%CI: 0.19-2.51) (Figure 7). All of the remaining four studies excluded from meta-analysis demonstrated a point estimate of null value (e-Table 4). A multivariate analysis reported by one study demonstrated that WBC was significantly associated with all-cause mortality of AE of IPF with an OR of 1.38 (95%CI: 1.04-1.83) (Yamazoe 2018 [70]) (e-Table 5).

A total of four studies reported oxygen therapy before AE using univariate analysis and the results of all these studies were combined. Based on the combined result, oxygen therapy before AE was significantly associated with all-cause mortality of AE of IPF with an HR of 1.88 (95%CI: 1.15-3.09) (Figure 8). A multivariate analysis reported by two studies demonstrated that oxygen therapy before AE was significantly associated with all-cause mortality of AE of IPF with HRs of 3.68 (95%CI: 1.05-12.9) (Enomoto 2018 [42]) and 2.34 (95%CI: 1.04-5.28) (Sokai 2017 [62]), respectively (e-Table 5).

Additional analysis

There was substantial heterogeneity in the result of meta-analysis using an MD for PaO2/FiO2 ratio (chi^2=32.91, p<0.00001, I^2=91%) (Figure 4). There was no variability in the location of study, the number of participants and diagnostic criteria for AE. All studies were conducted in Japan and included 50 or fewer patients who were diagnosed by nearly the same criteria. However, the effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. Meta-analysis excluding this study generated a significant result with an MD of -117.7 (95%CI: -148.0--87.5) and no heterogeneity was identified (chi^2=1.69, p=0.43, I^2=0%) (e-Figure 21).

Two additional subgroup analyses were conducted for non-prognostic factors (e-Figure 15, 17) but sensitivity analysis was not undertaken due to the small number of studies with low risk of bias. Small study bias including publication bias could not be assessed because the designated minimum number of studies (≥10) was not available for meta-analysis of any prognostic factor.

Quality of evidence

The GRADE system rated the quality of evidence for identified prognostic factors as either low or very low (e-Table 6).

Discussion

This systematic review and meta-analysis elucidated clinical information predictive of all-cause mortality of AE of IPF based on both univariate and multivariate analyses. These prognostic factors consisted of APACHE II score, PaO2/FiO2 ratio, LDH, WBC and oxygen therapy before AE. The knowledge of prognostic factors, which are composed of clinical information that is easily accessible in daily clinical practice, will be of great help in developing therapeutic strategies for this intractable disease and can be very informative to patients and families in facilitating their decision-making.

Among the identified prognostic factors in this study, oxygen therapy before the development of AE suggests that the disease has already been in an advanced stage and there remains the limited capacity of the lung. The PaO2/FiO2 ratio reflects the extent of the damage to the pulmonary parenchyma and the severity of the disease. LDH is a ubiquitous molecule distributed over the body and increases in bloodstream after tissue

destruction.[72] Accordingly, a higher value of LDH may indicate extensive damage in the lung although LDH is not a specific marker for pulmonary disease. A non-specific inflammatory maker such as WBC elevates when the body is exposed to external stressful circumstances.[73] Therefore, an elevation of WBC may reflect the severity of the disease although it may possibly be an indicator of occult infection that could not be identified by ordinary diagnostic procedures. Acute physiologic scoring system such as APACHE II score is usually applied to in-patients in intensive care unit to assess the severity of their conditions. It is an established tool and known to correlate to the prognosis of the disease.[74] Although this system is composed of multiple factors that are not directly caused by the disease localized to the lung, such as renal dysfunction and electrolyte disturbance, the wide range of respiratory indexes is also included as its components. As a result, a higher value of APACHE II score may indicate respiratory distress caused by severely damaged pulmonary parenchyma.

Overall, all of these prognostic factors are indicating progressive or severe disease state. They are analogous to those of other IPs.[75-76] In particular, oxygenation at presentation is reported to be predictive of the prognosis of the disease.[18] However, pulmonary function was not deemed as a prognostic factor in this study. This difference may suggest that the severity of the insult at the onset of AE is more closely associated with the subsequent clinical course of the disease. On the other hand, pulmonary state before AE may foretell the development of this devastating condition.[77] There was also no association between radiological findings and all-cause mortality of AE of IPF in this review and this was inconsistent with the reports of other IPs.[75-76] In contrast to the implication of baseline pulmonary function, radiological findings at the development of AE may directly reflect the damaged area of pulmonary parenchyma. AE of IPs can be pathologically classified into diffuse alveolar damage (DAD), organizing pneumonia (OP) and fibroblastic foci.[78] The prognosis of AE is reported to be closely related to these pathological patterns. In short, DAD demonstrates the worst prognosis.[79] However, these pathological findings are not necessarily correlated to radiological findings.[80] This may account for the finding of this review that no radiological findings were deemed as prognostic of all-cause mortality of AE of IPF.

The methodology of this review may have affected the selection and confirmation of prognostic factors although it had been reported in a protocol paper beforehand.[21] Potential prognostic factors were defined as any clinical information reported in three or more studies assuming that frequent reports would likely imply clinical relevance.

However, this arbitrary definition may have missed other potential prognostic factors. In addition, prognostic factors were confirmed by the results of both univariate and multivariate analyses based on statistical significance and the effect estimates in the same direction in the majority of included studies. However, multivariate analysis was conducted in a small number of studies. As a result, all of the prognostic factors in this review were determined based on the results of only a few or several studies, which may have turned out to be statistically significant by chance or non-significant due to low statistical power.

There is also some caveat that needs to be kept in mind to interpret the findings of this review. First, each study included in this review reported all-cause mortality at an arbitrary point in time such as in-hospital, 30 days, 90 days and overall. However, subgroup analysis was limited due to a small number of studies included for meta-analysis. Instead, causative clinical and/or methodological differences were sought to be identified qualitatively if there was statistically significant heterogeneity between studies. Second, most of the studies in this review were conducted in Japan. This finding may be related to the fact that AE of IPF was first reported by Japanese research group [7] and subsequently investigated vigorously in Japan.[81] In addition, it is reported that Japanese patients would more frequently develop progressive IP secondary to other medical conditions such as connective tissue disease [82] and drug toxicity.[83] Therefore, it is possible that Japanese people may be genetically more susceptible to AE of IPF, which may have led to more reports from Japan although the incidence of AE is reported to be similar between ethnicities.[84] However, this unbalanced report will limit an applicability of the findings of this review as they were mostly derived from data of Japanese patients. Therefore, further research needs to be conducted in other countries or regions to confirm the generalizability of the result of this study. Finally, the quality of evidence of this review was deemed low or very low for all prognostic factors by the GRADE system. This is because of methodological shortcomings in all studies and publication bias, which was assumed to be present in prognostic studies.[34] Therefore, further research of high quality is imperative to make a definitive conclusion.

Conclusion

This systematic review and meta-analysis demonstrated that APACHE II score, PaO2/FiO2 ratio, LDH, WBC and oxygen therapy before AE were deemed as prognostic factors of AE of IPF. However, the findings should be interpreted with

caution because the quality of evidence was rated low or very low and the applicability is mostly restricted to Japanese patients.

Ethics approval and participant consent

Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Data sharing

The dataset used and/or analyzed for this review will be available from the corresponding author upon a reasonable request and may become open to the public through a digital repository (such as Dryad) after the final result is published in a journal.

Conflict of interest

None to declare.

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Authors' contributions

H.K. planned the entire research project and analysed the data. He also summarized the result and wrote the manuscript. H.K. has full access to the data and takes responsibility for its integrity as well as the accuracy of the analysis.

O.M.P. contributed to the design of the research project and conducted the literature search and data extraction. He was also involved in revising the manuscript.

All researchers provided thoughts and opinions to compile a draft paper with revisions and then approved of the final version of the manuscript.

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e-Table 1 Characteristics of 37 studies included for the review

Study	Country	Study design	Patients (n) (M/F)	Age (years)[a]	Smoking (n (%))	Follow-up lengths	Outcome	Number of deaths (%)[b]
Abe 2012 [35]	Japan	Case-control	73 (58/15)	67.5±8.2	Mean 937 (SD 658) (Smoking index)	-	All-cause mortality (3-month)	48 (65.8)
Akira 2008 [36]	Japan	Prospective cohort	58 (44/14)	Median 66 (Range 45-82)	43 (74.1)	-	All-cause mortality (In-hospital)	25 (43.1)
Anzai 2013 [37]	Japan	Case-control	50 (41/9)	71.0±7.1[c]	(74.0)	-	All-cause mortality (Overall)	29 (58.0)
Atsumi 2018 [38]	Japan	Retrospective cohort	59 (49/10)	Median 74 (IQR 66-78)	Median 800 (IQR 500-1200) (Brinkman index)	-	All-cause mortality (60-day)	54 (91.5)
Cao 2016 [39]	China	Case-control	30 (23/7)	65.0±9.4	9 (30.0)	-	All-cause mortality (Overall)	26 (86.7)
Collard 2010 [40]	Korea	Retrospective cohort	47 (36/11)	66.0±8.0	40 (85.1)	-	All-cause mortality (Overall)	24 (51.1)
Enomoto 2015 [41]	Japan	Retrospective cohort	31 (28/3)	Median 69 (Range 50-84)	27 (87.1)	Median 53 months (Range 2-205)	All-cause mortality (3-month/12-month)	12 (38.7) (3 months) 23 (74.2) (12 months)
Enomoto 2018 [42]	Japan	Retrospective cohort	37	-	-	-	All-cause mortality (3-month)	10 (27.0)
Enomoto 2019 [43]	Japan	Retrospective cohort	37	-	-	-	All-cause mortality (3-month)	7 (18.9)
Fujimoto 2012 [44]	Japan	Retrospective cohort	60 (49/11)	Median 71 (IQR 63-75)	48 (80.0)	Median 370 days (Range 39-1230)	Disease-related mortality (Overall)	48 (80.0)

Furuya 2017 [45]	Japan	Retrospective cohort	47 (42/5)	Range 64-84	-	Median 173 days (Range 4-1137)	All-cause mortality (Overall)	27 (57.4)
Isshiki 2015 [46]	Japan	Retrospective cohort	41 (36/5)	72.6±6.4	36 (87.8)	Median 12 months (Range 1-143)	All-cause mortality (Overall)	29 (70.7)
Kang 2018 [47]	Korea	Case-control	66 (36/30)	70.8±9.0[c]	30 (45.5)	-	All-cause mortality (In-hospital)	29 (43.9)
Kataoka 2015 [48]	Japan	Case-control	40 (36/4)	Mean 72 (IQR 66-78)	-	-	All-cause mortality (3-month)	19 (47.5)
Kawamura 2017 [49]	Japan	Retrospective cohort	85 (66/19)	Median 76 (IQR 70-80)	-	-	All-cause mortality (60-day)	43 (50.6)
Kim 2006 [50]	Korea	Case-control	11	63.4±6.3 (n=8)	6 (75.0) (n=8)	-	All-cause mortality (In-hospital)	7 (63.6)
Kishaba 2018 [51]	Japan	Retrospective cohort	65 (40/25)	74.7±11.3	37 (56.9)	-	All-cause mortality (3-month)	-
Kishaba 2014 [52]	Japan	Retrospective cohort	58 (38/20)	75.0±9.6	58 (100.0)	Median 10.2 months (Range 0.1-112)	All-cause mortality (3-month)	- (70.7)
Koyama 2017 [53]	Japan	Case-control	47 (42/5)	Median 74 (Range 58-86)	42 (89.4)	-	All-cause mortality (3-month) Quality of life	19 (40.4)
Lee 2012 [54]	Korea	Retrospective cohort	24 (19/5)	64.3±9.4[c]	19 (79.2)	Median 74 days (IQR15-492)	All-cause mortality (Overall)	20 (83.3)
Nikaido 2018 [55]	Japan	Case-control	21 (21/0)	69.7±6.7[c]	-	-	All-cause mortality (60-day)	7 (33.3)

Novelli 2016 [56]	Italy	Retrospective cohort	11 (7/4)	Median 65 (IQR 55-75)	8 (72.7)	Median 18 months	All-cause mortality (3-month)	- (27.0)
Oishi 2016 [57]	Japan	Retrospective cohort	50 (46/4)	71.7±6.1	42 (84.0)	Median 42 days (Range 1-1656)	Disease-related mortality (Overall)	38 (76.0)
Papiris 2015 [58]	Greece	Retrospective cohort	17	-	-	-	All-cause mortality (Overall)	11 (39.3)
Sakamoto 2018 [59]	Japan	Retrospective cohort	80 (68/12)	72.9±6.3	67 (83.8)	Median 13 months (Range 1-137)	All-cause mortality (3-month)	- (46.3)
Sand 2018 [60]	Japan	Retrospective cohort	28 (28/0)	71.0±7.0	23 (82.1)	-	All-cause mortality (Overall)	13 (46.4) (at 100 days)
Saraya 2018 [61]	Japan	Retrospective cohort	27 (18/9)	Median 74 (IQR 70-84)	16 (66.7) (n=24)	-	All-cause mortality (60-day)	8 (29.6)
Sokai 2017 [62]	Japan	Retrospective cohort	59 (54/5)	71.7±8.2	49 (83.1)	-	All-cause mortality (180-day)	- (59.2)
Song 2011 [63]	Korea	Case-control	90 (69/21)	65.3±7.9	59 (65.6)	-	All-cause mortality (In-hospital)	45 (50.0)
Suzuki 2018 [64]	Japan	Retrospective cohort	62 (56/6)	Median 71 (IQR 64.8-76)	50 (80.6)	-	All-cause mortality (90-day)	32 (51.6)
Takei 2017 [65]	Japan	Case-control	18	-	-	-	All-cause mortality (90-day/Overall)	-
Tomioka 2007 [66]	Japan	Case-control	27 (18/9)	Mean 71 (Range 60-85)	20 (74.1)	-	All-cause mortality (In-hospital)	15 (55.6)
Tsushima 2014	Japan	Case-control	20 (14/6)	76.8±1.9[c]	-	-	All-cause mortality	7 (35.0)

[67]							(28-day)	
Vianello 2019	Italy	Retrospective	20 (15/5)	67.0±10.4[c]	9 (45.0)	Maximum 370 days	All-cause mortality	10 (50.0)
[68]		cohort					(In-ICU /Overall)	(In-ICU)
Woottoon 2011	Korea	Retrospective	43 (88%/12%)	Mean 65	(84.0)	-	All-cause mortality	- (51.2)
[69]		cohort					(60-day/Overall)	(60 days)
Yamazoe 2018	Japan	Retrospective	57		-	-	All-cause mortality	35 (61.4)
[70]		cohort					(In-hospital/Overall)	(In-hospital)
Yokoyama 2010	Japan	Case-control	11 (7/4)	72.3±7.7	8 (72.7)	-	All-cause mortality	6 (54.5)
[71]							(3-month)	

a, indicates mean±standard deviation unless otherwise specified; b, indicates the number of deaths at each point in time unless otherwise specified; c, calculated using the sample size and median, range or interquartile range in two comparative groups;

IQR, interquartile range;

e-Table 2 30 potential prognostic factors for all-cause mortality

Demographic characteristics
age, sex, smoking history, BMI, disease duration
Disease severity (staging) of underling IPF or acute phase
GAP system, JRS classification, APACHE II score
Symptoms
Duration of dyspnoea, fever
Pulmonary function tests (at baseline)
FVC, DLCO, FEV1
Radiological features
Pattern of distribution, GGO, reticular opacity, extent of abnormality
Laboratory findings
PaO2/FiO2 ratio, CRP, LDH, KL-6, SP-D, WBC, D-dimer, FDP, BAL lymphocyte, BAL neutrophil
Treatment before acute exacerbation
Pirfenidone, corticosteroid, oxygen therapy

APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; BMI, body mass index; CRP, C-reactive protein; DLCO, diffusion capacity of the lung for carbon monoxide; FDP, fibrin degradation product; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; HR, hazard ratio; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO2/FiO2, partial pressure of arterial oxygen/fraction of inspired oxygen; SP-D, surfactant protein-D; WBC, white blood cell;

e-Table 3 Risk of bias in 37 studies included for the review, assessed by the Quality in Prognostic Studies tool[a]

Study	study participation	study attrition	prognostic factor measurement	outcome measurement	study confounding	statistical analysis and reporting
Abe 2012 [35]	**high risk**	low risk	**high risk**	low risk	**high risk**	**high risk**
Akira 2008 [36]	medium risk	low risk	low risk	low risk	medium risk	**high risk**
Anzai 2013 [37]	low risk	low risk	medium risk	low risk	medium risk	**high risk**
Atsumi 2018 [38]	low risk	low risk	low risk	low risk	medium risk	**high risk**
Cao 2016 [39]	medium risk	low risk	low risk	low risk	**high risk**	**high risk**
Collard 2010 [40]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Enomoto 2015 [41]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Enomoto 2018 [42]	medium risk	**high risk**	low risk	low risk	medium risk	**high risk**
Enomoto 2019 [43]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Fujimoto 2012 [44]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Furuya 2017 [45]	low risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Isshiki 2015 [46]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Kang 2018 [47]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Kataoka 2015 [48]	low risk	low risk	medium risk	low risk	**high risk**	medium risk
Kawamura 2017 [49]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Kim 2006 [50]	medium risk	low risk	**high risk**	low risk	medium risk	**high risk**
Kishaba 2018 [51]	low risk	**high risk**	medium risk	low risk	**high risk**	**high risk**

Kishaba 2014 [52]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Koyama 2017 [53]	low risk	low risk	medium risk	low risk	**high risk**	**high risk**
Lee 2012 [54]	low risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Nikaido 2018 [55]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Novelli 2016 [56]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Oishi 2016 [57]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Papiris 2015 [58]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Sakamoto 2018 [59]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Sand 2018 [60]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Saraya 2018 [61]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Sokai 2017 [62]	low risk	**high risk**	low risk	low risk	medium risk	medium risk
Song 2011 [63]	medium risk	low risk	medium risk	low risk	**high risk**	**high risk**
Suzuki 2018 [64]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Takei 2017 [65]	medium risk	low risk	low risk	low risk	**high risk**	**high risk**
Tomioka 2007 [66]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Tsushima 2014 [67]	medium risk	low risk	low risk	low risk	**high risk**	**high risk**
Vianello 2019 [68]	**high risk**	**high risk**	low risk	low risk	**high risk**	**high risk**
Woottoon 2011 [69]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Yamazoe 2018 [70]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Yokoyama 2010 [71]	medium risk	low risk	**high risk**	low risk	**high risk**	**high risk**

a, Text in bold refers to high risk of bias.

e-Table 4 The result of univariate analysis of potential prognostic factors for all-cause mortality

Potential prognostic factors[a]	Analysis	Studies (n)[b]	Subjects (n)	Point estimate (+/-)[c]	Result of meta-analysis and non-pooled studies (95% CI)[d]
Demographic features					
Age	Meta	8	405	4/2	HR 1.00 (0.98-1.02) (/1 year)
		3	236	3/0	OR 1.02 (0.98-1.05) (/1 year)
	Not pooled	Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.83) (year)
		Anzai 2013 [37]	50	1/0	MD 3.50 (-0.48-7.48) (year) (non-survivor vs. survivor)
		Tsushima 2014 [67]	20	0/1	***MD -4.30 (-6.04--2.56) (yaer) (non-survivor vs. survivor)***
Sex	Meta	7	377	3/4	HR 0.93 (0.65-1.34) (vs. female)
		5	306	3/2	OR 1.28 (0.74-2.21) (vs. female)
	Not pooled	Kishaba 2014 [52]	58	0/1	HR 0.90 (p=0.76)
Smoking history	Meta	3	145	2/1	HR 0.98 (0.35-2.75) (vs. never-smoker)
		4	243	3/1	OR 0.99 (0.59-1.67) (vs. never-smoker)
		3	116	1/1	HR 1.00 (0.89-1.11) (/10 pack-year)
	Not pooled	Atsumi 2018 [38]	59	0/1	HR 0.95 (0.88-1.02) (/200 Brinkman index)
		Kishaba 2014 [52]	58	1/0	***HR 1.01 (p=0.03) (pack-year)***
BMI	Not pooled	Kang 2018 [47]	66	0/1	MD -0.13 (-2.12-1.86) (non-survivor vs. survivor)
		Suzuki 2018 [64]	62	1/0	HR 1.04 (0.94-1.15) (/1 kg/m^2)
		Lee 2012 [54]	24	0/1	HR 0.93 (0.82-1.05)
Disease duration before AE	Not pooled	Papiris 2015 [58]	17	1/0	HR 1.01 (1.00-1.03)
		Enomoto 2019 [43]	37	-/-	HR 1.00 (p=0.82) (/1 month)
		Song 2011 [63]	90	0/1	OR 0.99 (0.98-1.01) (months)

		Akira 2008 [36]	58	1/0	MD 2.00 (-11.6-15.6) (months) (non-survivor vs. survivor)
		Novelli 2016 [56]	11	0/1	8 vs. 20 (months) (non-survivor vs. survivor)
Disease severity (staging) of underling IPF or acute phase					
GAP system[e]	Not pooled	Atsumi 2018 [38]	59	1/0	***HR 1.45 (1.10-1.93) (/1 point)***
		Enomoto 2018 [42]	37	1/0	HR 1.08 (0.48-2.44) (/1 stage)
		Sakamoto 2018 [59]	80	1/0	OR 1.64 (0.98-2.70) (/1)
JRS classification[f]	Not pooled	Atsumi 2018 [38]	59	1/0	***HR 1.50 (1.17-1.94) (/1 stage)***
		Enomoto 2018 [42]	37	1/0	HR 2.12 (0.86-5.23)
		Sakamoto 2018 [59]	80	1/0	OR 1.28 (0.53-3.13) (advanced (III, IV))
APACHE II score	Meta	3	194	3/0	***HR 1.09 (1.04-1.15)(/1 point)***
	Not pooled	Nikaido 2018 [55]	21	1/0	MD 2.80 (-1.19-6.79) (non-survivor vs. survivor)
Symptoms					
Duration of dyspnoea	Not pooled	Song 2011 [63]	90	0/1	***OR 0.94 (0.90-0.98) (days)***
		Kishaba 2014 [52]	58	1/0	HR 1.01 (p=0.65) (days)
		Kang 2018 [47]	66	0/1	MD -6.43 (-15.9-3.04) (days) (non-survivor vs. survivor)
Fever	Meta	3	206	2/1	OR 1.66 (0.74-3.70)
	Not pooled	Enomoto 2019 [43]	37	0/1	HR 0.51 (p=0.39)
Pulmonary function					
FVC	Meta	5	199	1/3	HR 0.99 (0.98-1.01) (/1% predicted value)
		3	193	1/0	OR 1.01 (0.99-1.02) (/1% predicted value)
DLCO	Meta	4	171	1/2	HR 0.99 (0.98-1.01) (/1% predicted value)
	Not pooled	Kang 2018 [47]	66	0/1	MD -6.38 (-15.8-3.04) (% predicted value) (non-survivor vs. survivor)

		Sakamoto 2018 [59]	80	1/0	OR 1.01 (0.98-1.03)
FEV1	Not pooled	Kang 2018 [47]	66	0/1	MD -4.36 (-14.1-5.37) (% predicted value) (non-survivor vs. survivor)
		Koyama 2017 [53]	47	0/1	MD -11.0 (-23.8-1.82) (% predicted value) (non-survivor vs. survivor)
		Papiris 2015 [58]	17	-/-	HR 1.00 (0.94-1.06) (% predicted value)
Features on HRCT					
Pattern	Not pooled	Kim 2006 [50]	11	1/0	OR 30.3 (0.96-959.6) (multifocal vs. peripheral)
		Anzai 2013 [37]	50	1/0	OR 8.00 (0.82-78.0) (diffuse+multifocal vs. peripheral)
		Sakamoto 2018 [59]	80	1/0	OR 1.39 (0.55-3.45) (diffuse)
		Akira 2008 [36]	58	1/0	***HR 5.39 (2.60-11.2) (diffuse+multifocal vs. peripheral)***
		Kawamura 2017 [49]	85	0/1	HR 0.41 (0.10-1.71) (multifocal)
GGO	Not pooled	Sokai 2017 [62]	59	1/0	HR 1.01 (0.99-1.03)
		Papiris 2015 [58]	17	1/0	HR 1.65 (0.74-3.70)
		Lee 2012 [54]	24	1/0	HR 1.03 (1.00-1.06) (GGO score)
Reticular opacity	Not pooled	Akira 2008 [36]	58	1/0	HR 1.03 (1.00-1.06) (reticulation and honeycombing (%))
		Lee 2012 [54]	24	0/1	HR 0.96 (0.91-1.01) (reticulation score)
		Kishaba 2014 [52]	58	1/0	HR 1.32 (p=0.06) (traction bronchiectasis and honeycombing score)
		Sokai 2017 [62]	59	0/1	HR 0.98 (0.95-1.02) (reticulation and honeycombing (%))
Extent of abnormality	Meta	3	120	3/0	HR 1.02 (1.00-1.05) (/1 score)
		Akira 2008 [36]	58	1/0	***HR 1.07 (1.04-1.10) (%)***
Laboratory findings					
PaO2/FiO2 ratio	Meta	6	325	0/5	***HR 0.95 (0.92-0.97) (/10 mmHg)***
		3	236	0/3	***OR 0.92 (0.89-0.95) (/10 mmHg)***

		4	118	0/4	MD -76.3 (-153.9-1.28) (non-survivor vs. survivor)
	Not pooled	Novelli 2016 [56]	11	0/1	195 vs. 240 (non-survivor vs. survivor)
		Sokai 2017 [62]	59	1/0	HR 1.45 (0.71-3.03) (≥200)
CRP	Meta	4	243	3/0	***HR 1.05 (1.02-1.08) (/1mg/dl)***
		6	242	7/0	***SMD 0.69 (0.19-1.18) (non-survivor vs. survivor)***
	Not pooled	Kishaba 2014 [52]	58	0/1	HR 0.98 (p=0.47) (mg/dl)
		Song 2011 [63]	90	1/0	***OR 1.09 (1.01-1.17) (mg/dl)***
		Sakamoto 2018 [59]	80	1/0	OR 1.05 (0.97-1.14) (mg/dl)
LDH	Meta	7	425	6/0	***HR 1.02 (1.01-1.02) (/10 IU/L)***
		4	118	4/0	***SMD 0.48 (0.11-0.84) (non-survivor vs. survivor)***
	Not pooled	Kang 2018 [47]	66	1/0	OR 1.02 (1.00-1.04)
		Sakamoto 2018 [59]	80	1/0	OR 1.01 (1.00-1.01) (IU/L)
KL-6	Meta	4	265	3/0	***HR 1.02 (1.01-1.04) (/100 U/mL)***
		4	118	2/2	MD -23.6 (-119.7-72.5) (×10 U/mL) (non-survivor vs. survivor)
	Not pooled	Kishaba 2014 [52]	58	1/0	***HR 2.01 (p=0.001) (IU/L)***
		Enomoto 2018 [42]	37	-/-	HR 1.00 (1.00-1.00) (U/mL)
		Collard 2010 [40]	47	0/1	OR 0.41 (0.06-2.93) (log unit)
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (1.00-1.00) (U/mL)
SP-D	Meta	4	243	0/2	HR 0.99 (0.99-1.00) (/10 ng/ml)
	Not pooled	Anzai 2013 [37]	50	1/0	MD 25.0 (-155.6-205.6) (non-survivor vs. survivor) (ng/ml)
		Nikaido 2018 [55]	21	1/0	MD 172.2 (-76.3-420.7) (non-survivor vs. survivor) (ng/ml)
		Collard 2010 [40]	47	1/0	OR 1.23 (0.36-4.21) (log ng/ml)
		Sakamoto 2018 [59]	80	1/0	OR 1.01 (1.00-1.01) (ng/ml)

WBC	Meta	6	242	5/1	***MD 1.35 (0.19-2.51) (×10⁶/mm³) (non-survivor vs. survivor)***
	Not pooled	Kataoka 2015 [48]	40	-/-	OR 1.00 (1.00-1.00) (/mm³)
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (1.00-1.00) (/mm³)
		Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.47) (/mm³)
		Enomoto 2019 [43]	37	-/-	***HR 1.00 (p=0.03) (/ul)***
D-dimer	Not pooled	Suzuki 2018 [64]	62	1/0	***HR 1.03 (1.01-1.05) (/1 μg/ml)***
		Sakamoto 2018 [59]	80	0/1	OR 0.99 (0.94-1.04) (mg/ml)
		Nikaido 2018 [55]	21	1/0	MD 3.10 (-7.48-13.7) (μg/ml) (non-survivor vs. survivor)
FDP	Not pooled	Nikaido 2018 [55]	21	1/0	MD 3.0 (-21.6-27.6) (μg/ml) (non-survivor vs. survivor)
		Tsushima 2014 [67]	20	1/0	***MD 115.6 (73.5-157.7) (μg/ml) (non-survivor vs. survivor)***
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (0.98-1.02) (μg/ml)
BAL lymphocyte	Not pooled	Song 2011 [63]	90	0/1	***OR 0.91 (0.83-0.99) (%)***
		Suzuki 2018 [64]	62	0/1	HR 0.97 (0.92-1.01) (/1%)
		Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.97)
BAL neutrophil	Not pooled	Song 2011 [63]	90	1/0	OR 1.06 (1.00-1.12) (%)
		Suzuki 2018 [64]	62	1/0	***HR 1.01 (1.00-1.03) (/1%)***
		Kishaba 2014 [52]	58	0/1	HR 0.94 (p=0.33)
Treatment before AE					
Pirfenidone	Meta	3	164	3/0	HR 1.34 (0.81-2.24)
		Sakamoto 2018 [59]	80	0/1	OR 0.85 (0.28-2.56)
Corticosteroid	Meta	3	161	2/1	HR 0.96 (0.61-1.52)
		Song 2011 [63]	90	0/1	OR 0.83 (0.35-1.94) (corticosteroid with or without cytotoxic agent)

		Sakamoto [59]	80	1/0	OR 1.75 (0.64-4.76)
Oxygen therapy	Meta	4	160	4/0	***HR 1.88 (1.15-3.09)***

a, Text in italic bold refers to potential prognostic factors, which demonstrated consistent and statistically significant results in the majority of studies. If the result of meta-analysis was significant, all studies included for the analysis were assumed to be significant to determine whether the majority of studies demonstrated significant results.

b, The number of included studies was described for meta-analysis while an individual study was specified for non-pooled studies.

c, Plus (+) indicates a positive association between mortality and potential prognostic factors based on point estimates while minus (-) indicates the negative association. Studies with null effects such as zero by MDs and one by HRs were not counted in this column. The direction of point estimates of all pooled and non-pooled studies were considered.

d, Parenthesis indicates 95% confidence interval unless otherwise specified. Text in bold refers to statistically significant results. Per unit for relative values such as ORs and HRs was described only if data was available and otherwise only unit was described.

e, The system considers gender, age and two lung physiology variables, i.e., FVC and DLCO. Points are assigned to each component of the system and there are three stages depending on the total points with a higher value indicating severer disease.

f, The classification consists of PaO_2 at rest and minimum SpO_2 during the six-minute walking test. There are four stages based on a combination of the value of both PaO2 and SpO2 with a higher stage indicating severer disease.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FDP, fibrin degradation product; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; HR, hazard ratio; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; Meta, meta-analysis; OR, odds ratio; PaO_2, partial pressure of

arterial oxygen; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio, SMD, standardized mean difference; SP-D, SpO2, saturation of percutaneous oxygen; surfactant protein-D; WBC, white blood cell;

e-Table 5 The result of multivariate analysis of potential prognostic factors for all-cause mortality

Potential prognostic factors[a]	Studies (n)	Subjects (n)	Effect estimates (95% CI)[b]
Demographic features			
Age	Akira 2008 [36]	58	HR 1.00 (0.96-1.04) (year)
	Kang 2008 [47]	66	OR 0.97 (0.91-1.04) (year)
	Yamazoe 2018 [70]	57	OR 0.96 (0.87-1.07) (year)
Sex	Akira 2008 [36]	58	HR 0.91 (0.34-2.43) (vs. female)
Smoking history	Akira 2008 [36]	58	HR 2.47 (0.91-6.70) (vs. never-smoker)
	Sokai 2017 [62]	59	HR 0.51 (0.23-1.31)
Disease severity (staging) of underling IPF or acute phase			
GAP system[c]	Atsumi 2018 [38]	59	HR 0.98 (0.62-1.51) (/1 point)
APACHE II score	Kawamura 2017 [49]	85	***HR 1.10 (1.10-1.19)***
Symptoms			
Fever	Kang 2018 [47]	66	OR 1.35 (0.41-4.50)
Pulmonary function			
FVC	Akira 2008 [36]	58	HR 0.98 (0.96-1.01) (% predicted value)
	Kang 2018 [47]	66	OR 1.00 (0.96-1.04) (% predicted value)
DLCO	Akira 2008 [36]	58	HR 1.02 (1.00-1.04) (% predicted value)
Features on HRCT			
Pattern	Akira 2008 [36]	58	***HR 4.63 (1.90-11.3)*** (diffuse+multifocal vs. peripheral)
GGO	Sokai 2017 [62]	59	HR 0.99 (0.96-1.02)
Extent of abnormality	Akira 2008 [36]	58	***HR 1.07 (1.02-1.12) (%)***
	Atsumi 2018 [38]	59	HR 1.18 (0.99-1.39) (/10 score)
	Enomoto 2018 [42]	37	***HR 1.22 (1.01-1.48) (score)***
Laboratory findings			
PaO2/FiO2 ratio	Kang 2018 [47]	66	***OR 0.99 (0.98-1.00)***
	Yamazoe 2018 [70]	57	OR 1.00 (0.99-1.01)
	Kishaba 2018 [51]	65	***HR 0.99 (0.99-1.00)***
	Suzuki 2018 [64]	62	***HR 0.31 (0.14-0.67) (>300 vs. ≤300)***
	Sakamoto 2018 [59]	80	***OR 0.99 (0.99-1.00)***
CRP	Song 2011 [63]	90	***OR 2.47 (1.03-5.91) (mg/dl)***
	Yamazoe 2018 [70]	57	OR 1.00 (0.90-1.13) (mg/dl)
	Kataoka 2015 [48]	40	OR 1.18 (1.00-1.39) (mg/dl)

LDH	Kang 2018 [47]	66	OR 1.00 (1.00-1.00)
	Akira 2008 [36]	58	***HR 1.002 (1.000-1.004)***
	Kishaba 2018 [51]	65	***HR 1.003 (1.001-1.005) (IU/L)***
	Enomoto 2018 [42]	37	***HR 1.01 (1.00-1.01) (IU/L)***
KL-6	Suzuki 2018 [64]	62	***HR 1.24 (1.05-1.46) (/500U/mL)***
	Sokai 2017 [62]	59	***HR 1.02 (1.00-1.05) (/100U/mL)***
WBC	Yamazoe 2018 [70]	57	***OR 1.38 (1.04-1.83) (/μl)***
D-dimer	Suzuki 2018 [64]	62	***HR 1.04 (1.02-1.06) (/1/μg/mL)***
BAL lymphocyte	Song 2011 [63]	90	OR 0.87 (0.74-1.02) (%)
BAL neutrophil	Sokai 2017 [62]	59	***HR 1.02 (1.00-1.03) (%)***
Treatment before AE			
Oxygen therapy	Enomoto 2018 [42]	37	***HR 3.68 (1.05-12.9)***
	Sokai 2017 [62]	59	***HR 2.34 (1.04-5.28)***

a, Text in italic bold refers to potential prognostic factors, which demonstrated consistent and statistically significant results in the majority of studies.

b, Parenthesis indicates 95% confidence interval unless otherwise specified. Text in bold refers to statistically significant results. Per unit for relative values such as ORs and HRs was described only if data was available and otherwise only unit was described.

c, The system considers gender, age and two lung physiology variables, i.e., FVC and DLCO. Points are assigned to each component of the system and there are three stages depending on the total points with a higher value indicating severer disease.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; CRP, C-reactive protein; CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; HR, hazard ratio; HRCT, high resolution computed tomography; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; OR, odds ratio; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen, WBC, white blood cell

e-Table 6 Assessment of quality of evidence of prognostic factors by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Outcome: all-cause mortality										
			GRADE factors							
Prognostic factors[a]	Analysis[b]	Phase	Study limitations	Inconsistency[c]	Indirectness	Publication bias	Imprecision	Moderate/large effect size	Dose effect	Overall quality
APACHE II score	Uni	1	+	-	-	+	-	-	-	Very Low
	Multi	1	+	N/A	-	+	-	-	-	Very low
PaO2/FiO2 ratio	Uni	1	+	-	-	+	-	+	-	Low
	Multi	1	+	-	-	+	-	-	-	Very low
LDH	Uni	1	+	-	-	+	-	-	-	Very low
	Multi	1	+	-	-	+	-	-	-	Very low
WBC	Uni	1	+	-	-	+	-	-	-	Very low
	Multi	1	+	N/A	-	+	-	-	-	Very low
Oxygen therapy	Uni	1	+	-	-	+	-	-	-	Very low
(before AE)	Multi	1	+	-	-	+	+	+	-	Very low

a, A total of 5 clinical information was determined as prognostic factors from 30 potential prognostic factors based on the consistent and significant result on both univariate and multivariate analyses.

b, ‘uni’ indicating univariate analysis while ‘multi’ indicating multivariate analysis.

c, N/A indicating not applicable due to only one study available.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; HRCT, high resolution computed tomography; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio, WBC, white blood cell;

Figure legends

Figure 1. Forrest plot of the result of univariate analysis for APACHE II score

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 194 patients were included. APACHE II score was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.09 (95% confidence interval: 1.04 to 1.15, p=0.0009). There was no heterogeneity (chi^2=0.95, p=0.62, I^2=0%).

Figure 2. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio (combined by hazard ratio)

The result of univariate analysis in 6 studies were pooled for meta-analysis and a total of 325 patients were included. PaO2/FiO2 ratio was significantly associated with all-cause mortality with a hazard ratio (HR) of 0.95 (95% confidence interval: 0.92 to 0.97, p<0.0001). There was no heterogeneity (chi^2=4.66, p=0.46, I^2=0%).

Figure 3. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio (combined by odds ratio)

The result of univariate analysis in 3 studies were pooled for meta-analysis and a total of 236 patients were included. PaO2/FiO2 ratio was significantly associated with all-cause mortality with an odds ratio (OR) of 0.92 (95% confidence interval: 0.89 to 0.95, p<0.00001). There was mild heterogeneity with no statistical significance (chi^2=2.46, p=0.29, I^2=19%). The 95% prediction interval ranged from 0.75 to 1.13.

Figure 4. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/ fraction of inspired oxygen (PaO2/FiO2) ratio (combined by mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. There was no significant difference of PaO2/FiO2 ratio between non-survivors and survivors with a mean difference (MD) of -76.3 mmHg (95% confidence interval: -153.9 to 1.28, p=0.05). There was substantial heterogeneity with statistical significance (chi^2=32.91, p<0.00001, I^2=91%). The 95% prediction interval ranged from -435.2 to 282.6. All studies were conducted in Japan and implemented nearly the same definition of AE of IPF. The number of included patients were 50 or fewer in all studies. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. It analysed 28-day all-cause mortality whereas the other three studies analysed either in-hospital, 60-day or overall all-cause mortality.

Figure 5. Forrest plot of the result of univariate analysis for lactate dehydrogenase (LDH) (combined by hazard ratio)

The result of univariate analysis in 7 studies was pooled for meta-analysis and a total of 425 patients were included. LDH was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.01 to 1.02, p<0.00001). There was no heterogeneity (chi^2=5.58, p=0.47, I^2=0%).

Figure 6. Forrest plot of the result of univariate analysis for lactate dehydrogenase (LDH) (combined by standardized mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. LDH was significantly associated with all-cause mortality with a standardized mean difference (SMD) of 0.48 (95% confidence interval: 0.11 to 0.84, p=0.01). There was no heterogeneity (chi^2=0.66, p=0.88, I^2=0%).

Figure 7. Forrest plot of the result of univariate analysis for white blood cell (WBC) count

The result of univariate analysis in 6 studies was pooled for meta-analysis and a total of 242 patients were included. WBC count was significantly associated with all-cause mortality with a mean difference (MD) of 1.35 (95% confidence interval: 0.19 to 2.51, p=0.02). There was mild heterogeneity with no statistical significance (chi^2=6.41, p=0.27, I^2=22%). The 95% prediction interval ranged from -1.15 to 3.85.

Figure 8. Forrest plot of the result of univariate analysis for oxygen therapy before acute exacerbation

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 160 patients were included. Oxygen therapy before acute exacerbation was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.88 (95% confidence interval: 1.15 to 3.09, p=0.01). There was no heterogeneity (chi^2=2.05, p=0.56, I^2=0%).

e-Figure legends

e-Figure 1. Study flow diagram

A total of 6763 reports were identified through Medline, EMBASE, Science Citation Index Expanded and Google Scholar. After excluding 1368 duplicates, 79 non-English records, 3293 reports of ineligible types (consisting of 1353 conference proceedings, 1068 review articles, 294 editorials or letters and 578 case reports) and 1917 irrelevant articles, the remaining 106 reports were obtained as full-texts. Out of these, 69 reports were excluded due to no prognosis in 43 studies, interstitial pneumonia other than IPF in 12 studies, deterioration other than acute exacerbation in 3 studies, inclusion of stable IPF in 5 studies, multiple episodes of acute exacerbation in 1 study and no quantitative data in 5 studies. Finally, 37 articles/studies were eligible for this review.

e-Figure 2. Forrest plot of the result of univariate analysis for age (combined by hazard ratio)

The result of univariate analysis in 8 studies was pooled for meta-analysis and a total of 405 patients were included. Age was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.00 (95% confidence interval: 0.98 to 1.02, p=0.92). There was no heterogeneity (chi^2=4.92, p=0.67, I^2=0%).

e-Figure 3. Forrest plot of the result of univariate analysis for age (combined by odds ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 236 patients were included. Age was not significantly associated with all-cause mortality with an odds ratio (OR) of 1.02 (95% confidence interval: 0.98 to 1.05, p=0.35). There was no heterogeneity (chi^2=0.34, p=0.84, I^2=0%).

e-Figure 4. Forrest plot of the result of univariate analysis for sex (male vs. female) (combined by hazard ratio)

The result of univariate analysis in 7 studies was pooled for meta-analysis and a total of 377 patients were included. Men were not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.93 (95% confidence interval: 0.65 to 1.34, p=0.71). There was no heterogeneity (chi^2=4.01, p=0.68, I^2=0%).

e-Figure 5. Forrest plot of the result of univariate analysis for sex (male vs. female) (combined by odds ratio)

The result of univariate analysis in 5 studies was pooled for meta-analysis and a total of 306 patients were included. Men were not significantly associated with all-cause mortality with an odds ratio (OR) of 1.28 (95% confidence interval: 0.74 to 2.21, p=0.38). There was no heterogeneity (chi^2=3.98, p=0.41, I^2=0%).

e-Figure 6. Forrest plot of the result of univariate analysis for smoking history (ever-smoker vs. never-smoker) (combined by hazard ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 145 patients were included. Smoking history was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.98 (95% confidence interval: 0.35 to 2.75, p=0.97). There was considerable heterogeneity with statistical significance (chi^2=5.88, p=0.05, I^2=66%). The 95% prediction interval ranged from 0.0000 to 95377. All studies were conducted in Japan and implemented nearly the same definition of AE of IPF. One study (Sokai 2017 [62]) demonstrated the effect estimate in the opposite direction from the other two studies. It included over 50 patients and analysed 180-day all-cause mortality whereas the other two studies included over 50 or fewer than 50 patients and analysed in-hospital or overall all-cause mortality.

e-Figure 7. Forrest plot of the result of univariate analysis for smoking history (ever-smoker vs. never-smoker) (combined by odds ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. Smoking history was not significantly associated with all-cause mortality with an odds ratio (OR) of 0.99 (95% confidence interval: 0.59 to 1.67, p=0.98). There was no heterogeneity (chi^2=0.49, p=0.92, I^2=0%).

e-Figure 8. Forrest plot of the result of univariate analysis for smoking history (pack-year)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 116 patients were included. Smoking history was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.00 (95% confidence interval: 0.89 to 1.11, p=0.93). There was mild heterogeneity with no statistical significance (chi^2=2.48, p=0.29, I^2=19%). The 95% prediction interval ranged from 0.51 to 1.97.

e-Figure 9. Forrest plot of the result of univariate analysis for fever

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 206 patients were included. Fever was not significantly associated with all-cause

mortality with an odds ratio (OR) of 1.66 (95% confidence interval: 0.74 to 3.70, p=0.22). There was considerable heterogeneity with statistical significance (chi^2=5.32, p=0.07, I^2=62%). The 95% prediction interval ranged from 0.0003 to 10770. All studies implemented the same definition of AE of IPF. One study (Anzai 2013 [37]), which was conducted in Japan, demonstrated the effect estimate in the opposite direction from the other two studies. It included 50 patients and analysed overall all-cause mortality. The other two studies, which were conducted in Korea, included over 50 patients and analysed in-hospital all-cause mortality.

e-Figure 10. Forrest plot of the result of univariate analysis for percentage of predicted value of forced vital capacity (%FVC) (combined by hazard ratio)

The result of univariate analysis in 5 studies was pooled for meta-analysis and a total of 199 patients were included. %FVC was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.98 to 1.01, p=0.29). There was no heterogeneity (chi^2=2.69, p=0.61, I^2=0%).

e-Figure 11. Forrest plot of the result of univariate analysis for percentage of predicted value of forced vital capacity (%FVC) (combined by odds ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 193 patients were included. %FVC was not significantly associated with all-cause mortality with an odds ratio (OR) of 1.01 (95% confidence interval: 0.99 to 1.02, p=0.49). There was no heterogeneity (chi^2=0.83, p=0.66, I^2=0%).

e-Figure 12. Forrest plot of the result of univariate analysis for percentage of predictive value of diffusion capacity of the lung for carbon monoxide (%DLCO)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 171 patients were included. %DLCO was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.98 to 1.01, p=0.42). There was no heterogeneity (chi^2=1.62, p=0.66, I^2=0%).

e-Figure 13. Forrest plot of the result of univariate analysis for extent of abnormality on high resolution computed tomography (HRCT) scan

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 120 patients were included. Extent of abnormality on HRCT scan was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.00 to 1.05, p=0.08). There was moderate heterogeneity with no statistical

significance (chi^2=2.88, p=0.24, I^2=30%). The 95% prediction interval ranged from 0.85 to 1.23.

e-Figure 14. Forrest plot of the result of univariate analysis for C-reactive protein (CRP) (combined by hazard ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. CRP was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.05 (95% confidence interval: 1.02 to 1.08, p=0.003). There was no heterogeneity (chi^2=1.14, p=0.77, I^2=0%).

e-Figure 15. Forrest plot of the result of univariate analysis for C-reactive protein (CRP) (combined by standardized mean difference)

The result of univariate analysis in 6 studies was pooled for meta-analysis and a total of 242 patients were included. CRP was significantly associated with all-cause mortality with a standardized mean difference (SMD) of 0.69 (95% confidence interval: 0.19 to 1.18, p=0.007). There was substantial heterogeneity (chi^2=16.44, p=0.006, I^2=70%). The 95% prediction interval ranged from -0.86 to 2.24. All studies except for one study (Kang 2018 [47]) were conducted in Japan and most of these studies included 50 or fewer patients. All studies implemented nearly the same definition of AE of IPF. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other five studies. It analysed 28-day all-cause mortality whereas the other five studies analysed either in-hospital, 60-day, 3-month or overall all-cause mortality. Meta-analysis excluding this study demonstrated a SMD of 0.45 (95%CI: 0.19-0.72) with no heterogeneity (chi^2=2.00, p=0.74, I^2=0%).

e-Figure 16. Forrest plot of the result of univariate analysis for Krebs von den Lungen-6 (KL-6) (combined by hazard ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 265 patients were included. KL-6 was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.01 to 1.04, p=0.008). There was no heterogeneity (chi^2=1.01, p=0.80, I^2=0%).

e-Figure 17. Forrest plot of the result of univariate analysis for Krebs von den Lungen-6 (KL-6) (combined by mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. KL-6 was not significantly associated with all-cause

mortality with a mean difference (MD) of -23.6 (95% confidence interval: -119.7 to 72.5, p=0.63). There was substantial heterogeneity with statistical significance (chi^2=18.13, p=0.0004, I^2=83%). The 95% prediction interval ranged from -458.7 to 411.5. All studies were conducted in Japan and included 50 or fewer patients. All studies implemented nearly the same definition of AE of IPF. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. It analysed 28-day all-cause mortality whereas the other three studies analysed either in-hospital, 60-day or overall all-cause mortality. Meta-analysis excluding this study demonstrated an MD of 31.3 (95%CI: -11.1 to 73.7) with no heterogeneity (chi^2=1.30, p=0.52, I^2=0%).

e-Figure 18. Forrest plot of the result of univariate analysis for surfactant protein-D (SP-D) (combined by hazard ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. SP-D was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.99 to 1.00, p=0.15). There was no heterogeneity (chi^2=0.20, p=0.98, I^2=0%).

e-Figure 19. Forrest plot of the result of univariate analysis for pirfenidone therapy before acute exacerbation

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 164 patients were included. Pirfenidone therapy before acute exacerbation was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.34 (95% confidence interval: 0.81 to 2.24, p=0.26). There was mild heterogeneity with no statistical significance (chi^2=2.27, p=0.32, I^2=12%). The 95% prediction interval ranged from 0.02 to 75.6.

e-Figure 20. Forrest plot of the result of univariate analysis for corticosteroid therapy before acute exacerbation

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 161 patients were included. Corticosteroid therapy before acute exacerbation was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.96 (95% confidence interval: 0.61 to 1.52, p=0.87). There was no heterogeneity (chi^2=1.65, p=0.44, I^2=0%).

e-Figure 21. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio (combined by mean difference)

As there was substantial heterogeneity in the result of meta-analysis using MD for PaO2/FiO2 ratio (Figure 4), meta-analysis was re-conducted after excluding one study (Tsushima 2014 [67]) that demonstrated an extremely different effect estimate from the other studies. The result was significant with an MD of -117.7 (95%CI: -148.0--87.5) and no heterogeneity was identified (chi^2=1.69, p=0.43, I^2=0%).

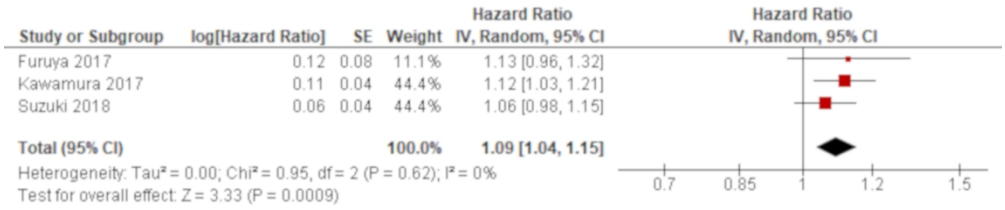

Figure 1

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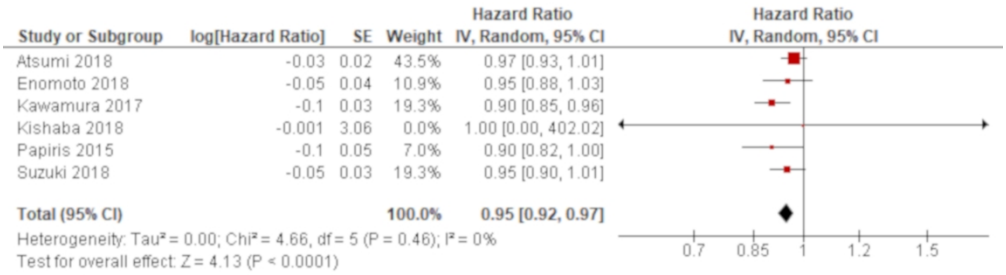

Figure 2

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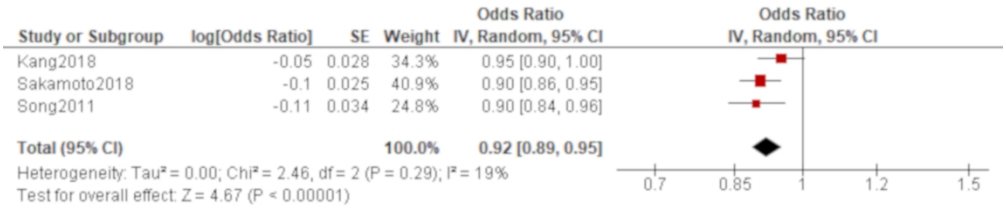

Figure 3

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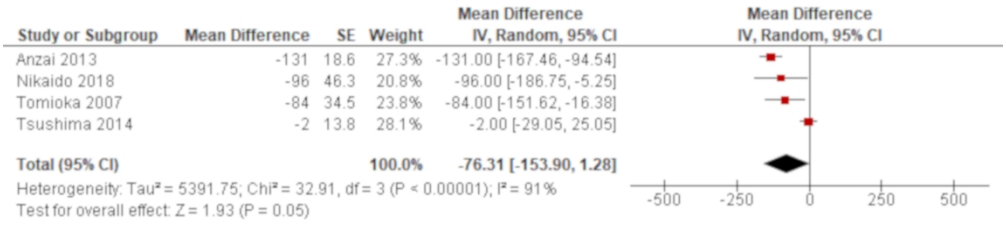

Figure 4

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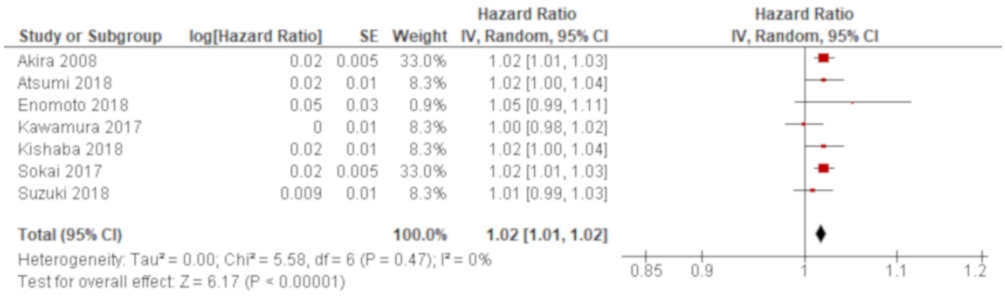

Figure 5

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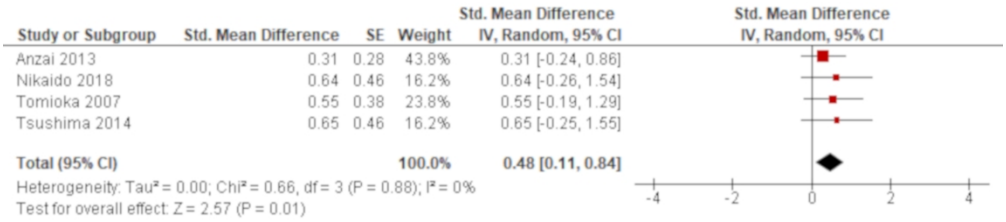

Figure 6

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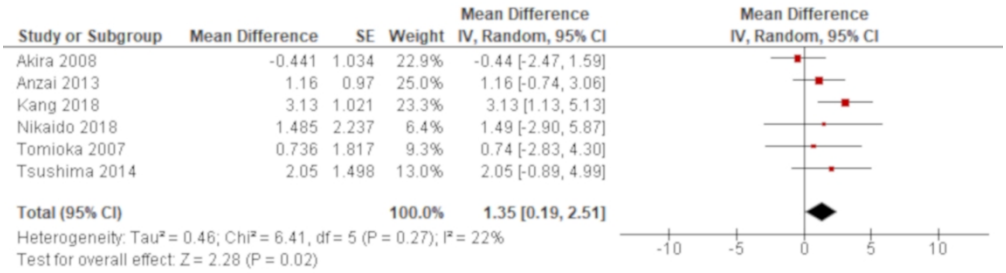

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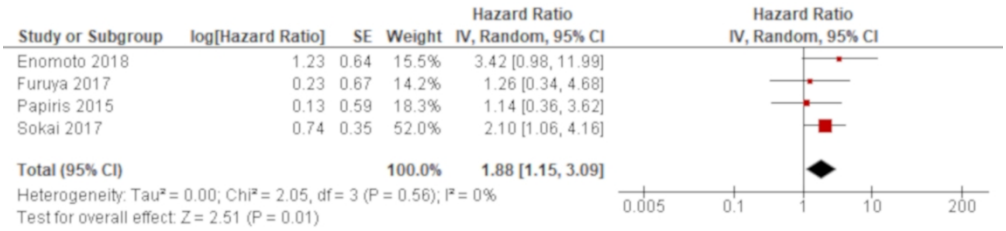

Figure 8

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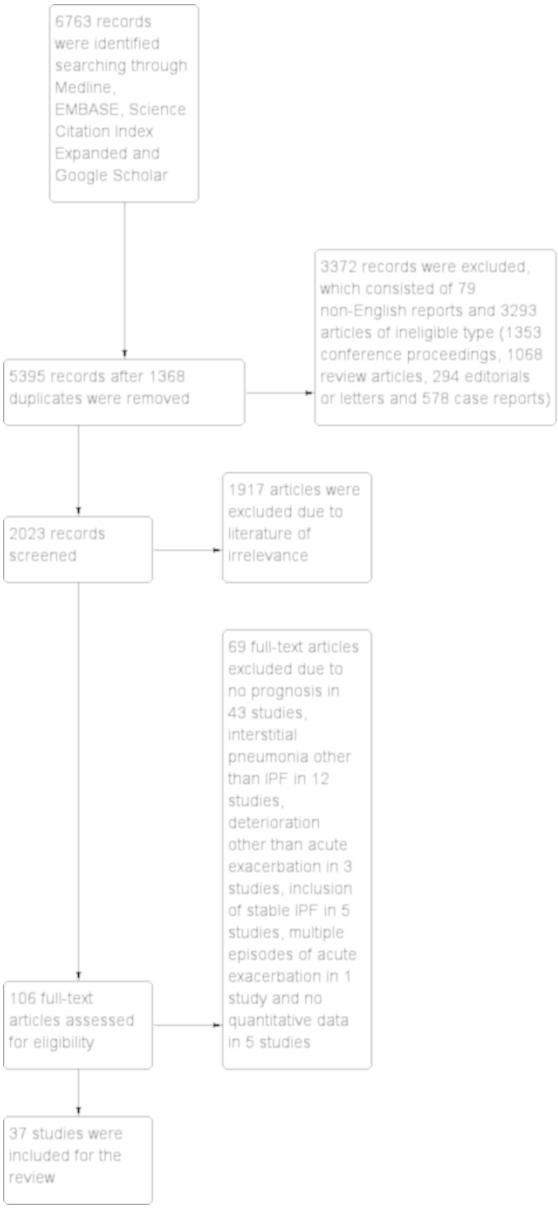

e-Figure 1

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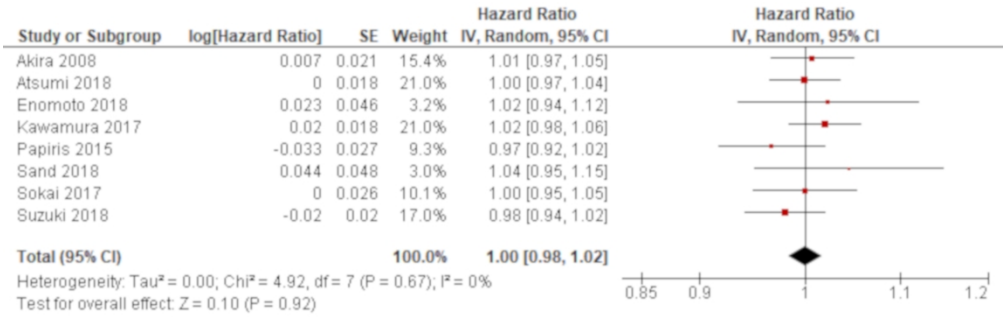

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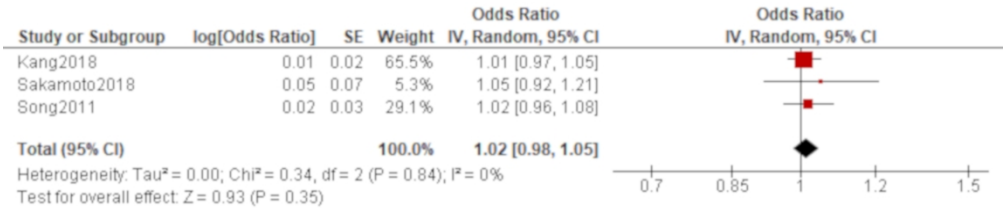

e-Figure 3

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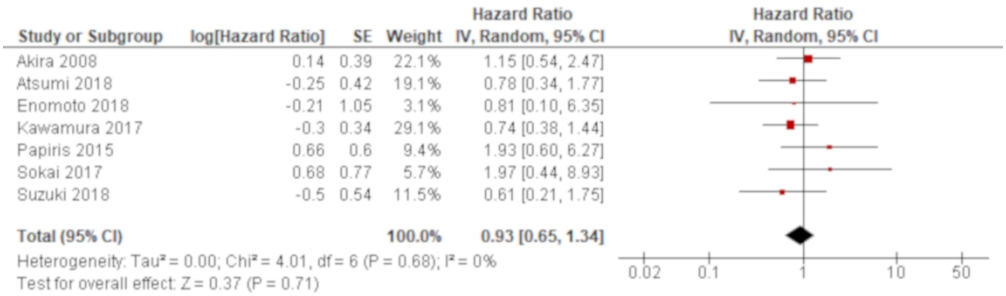

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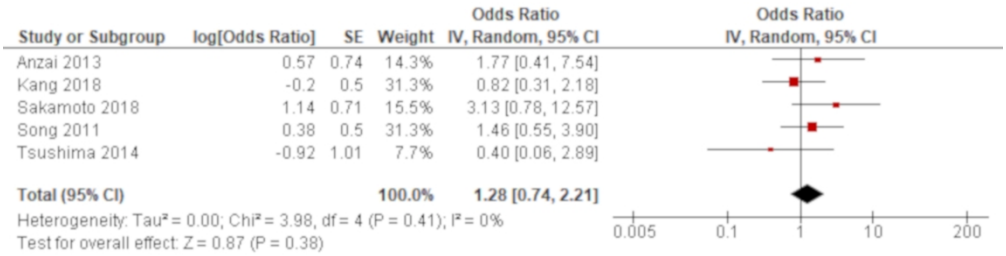

e-Figure 5

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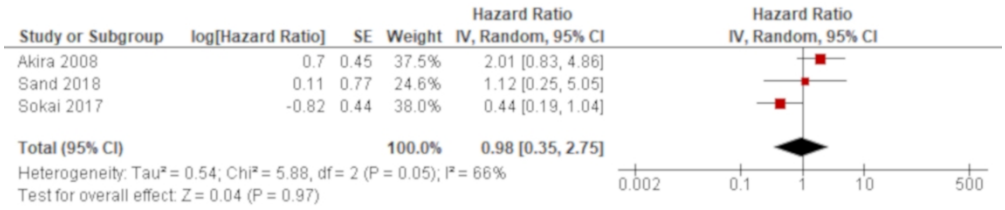

e-Figure 6

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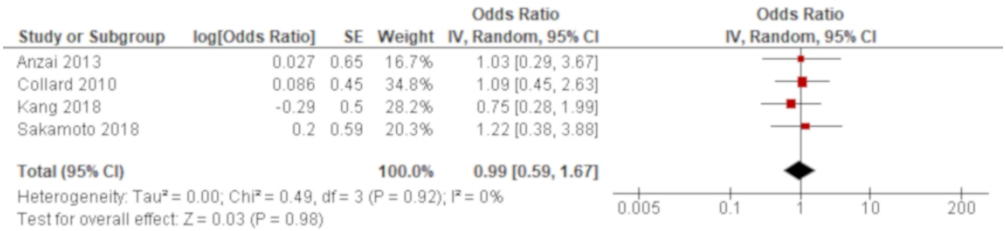

e-Figure 7

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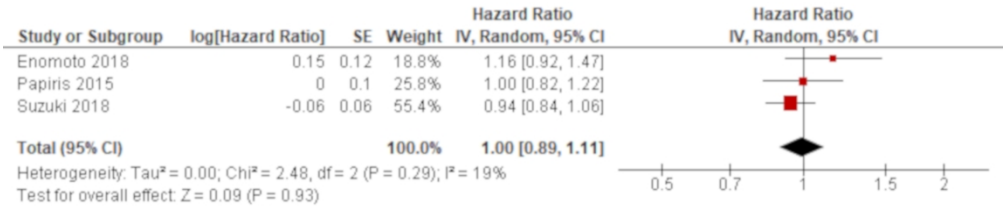

e-Figure 8

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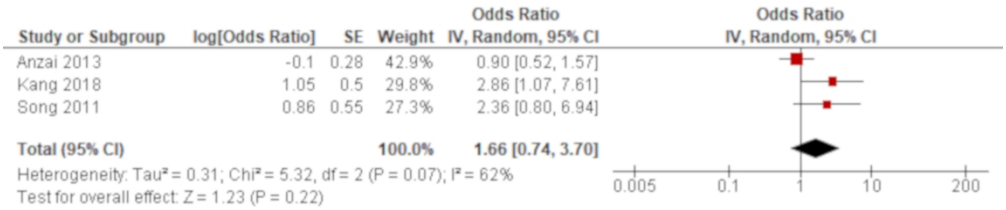

e-Figure 9

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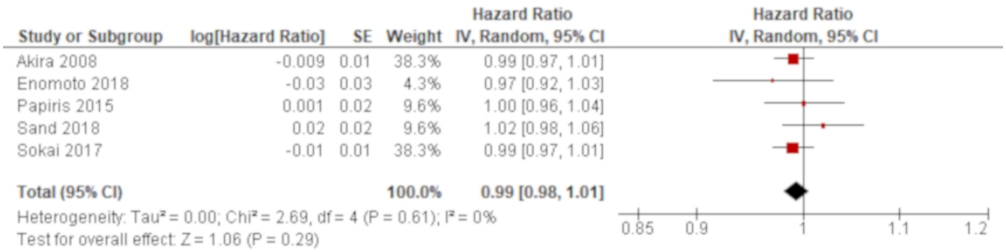

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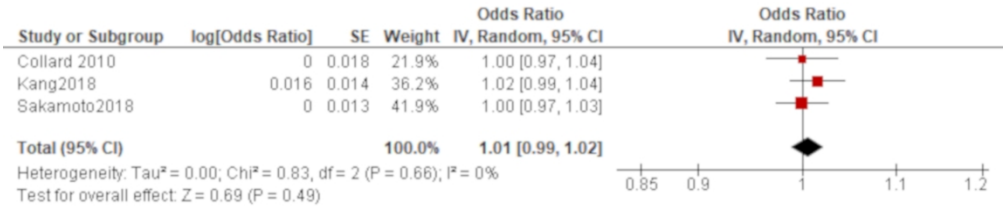

e-Figure 11

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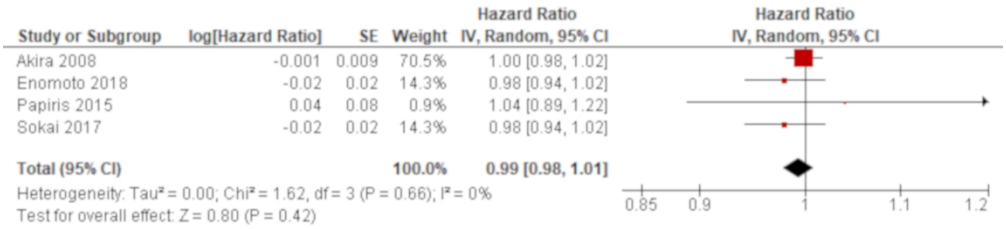

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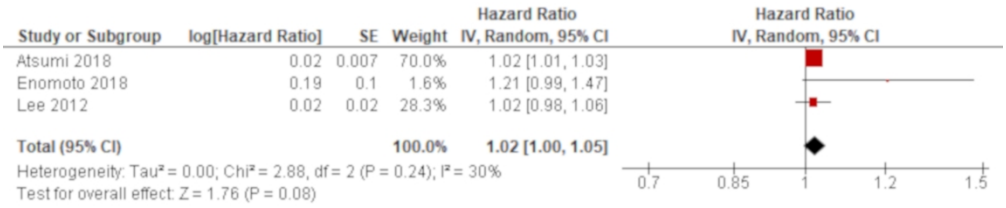

e-Figure 13

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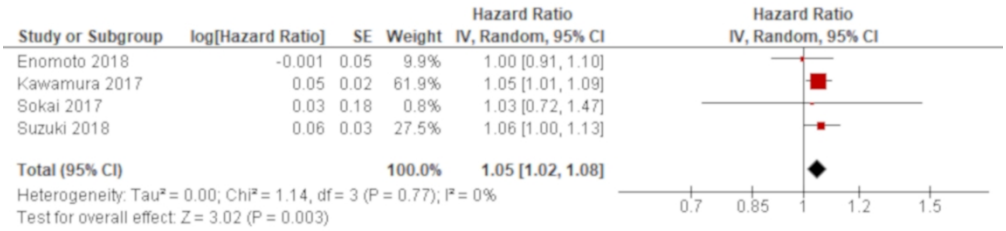

e-Figure 14

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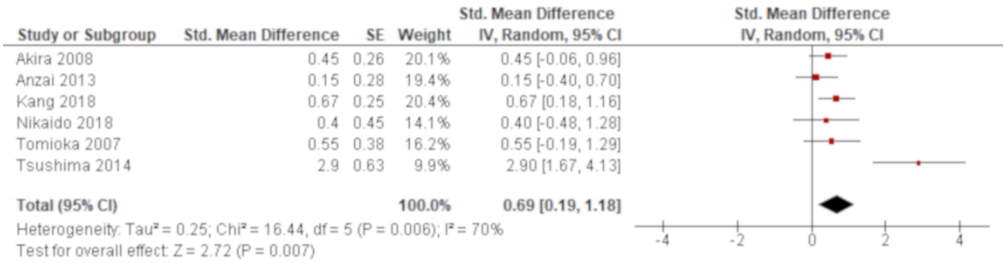

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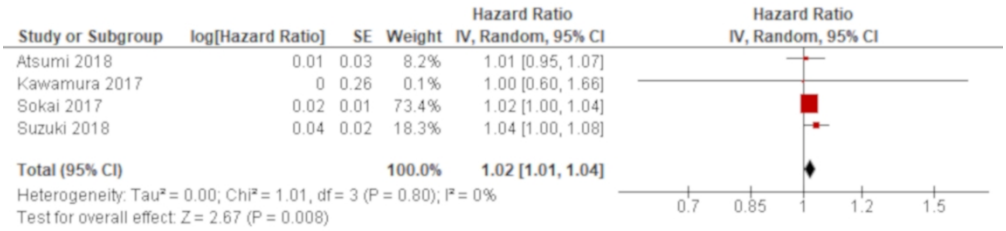

e-Figure 16

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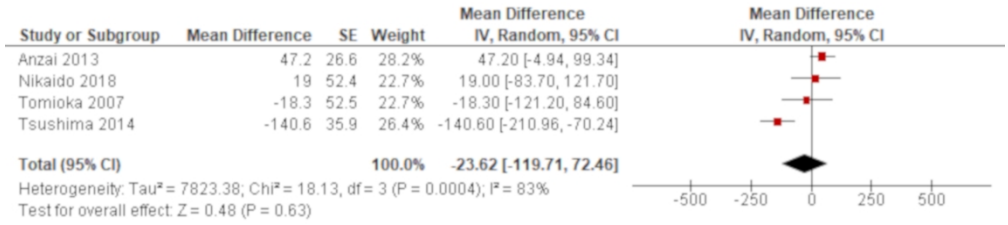

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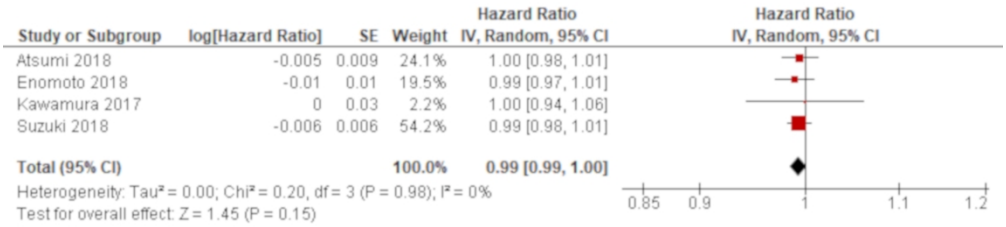

e-Figure 18

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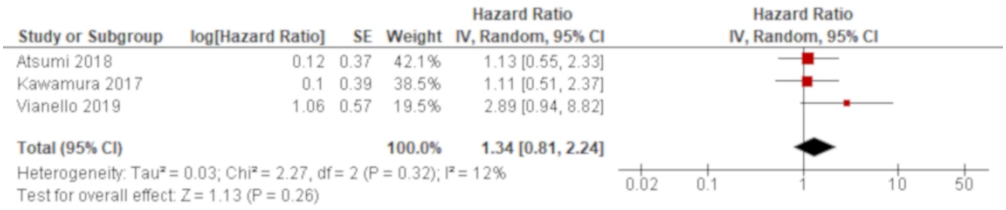

e-Figure 19

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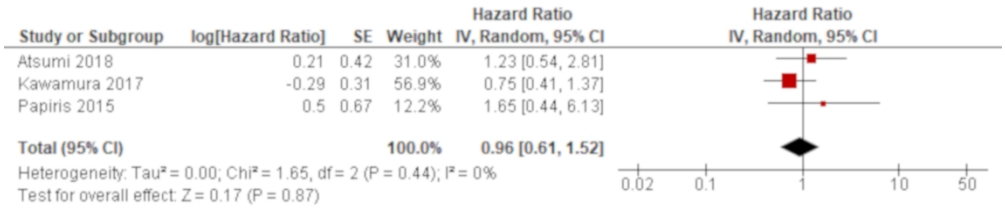

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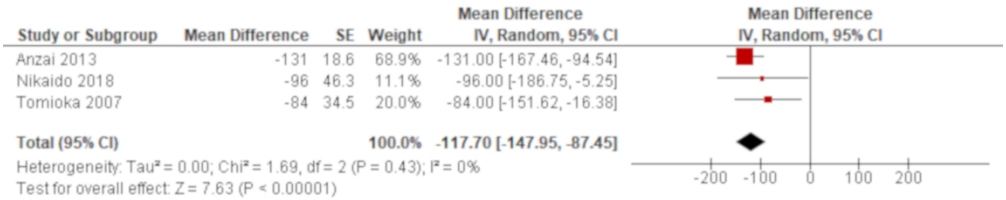

e-Figure 21

235x50mm (600 x 600 DPI)

e-Appendix: Search terms for each electronic database

Medline (Ovid)

1 exp Pulmonary Fibrosis/

2 exp Idiopathic Pulmonary Fibrosis/

3 exp Lung Diseases, Interstitial/

4 (pulmonary adj3 fibros$).mp.

5 (interstitial adj3 pneumoni$).mp.

6 exp Disease Progression /

7 (acute adj3 exacerbation?).mp.

8 (disease adj3 progression?).mp.

9 (disease adj3 exacerbation?).mp.

10 (deterioration?).mp.

11 incidence.sh.

12 exp Mortality/

13 follow-up studies.sh.

14 prognos$.tw.

15 predict$.tw.

16 course$.tw.

17 (1 or 2 or 3 or 4 or 5)

18 (6 or 7 or 8 or 9 or 10)

19 (11 or 12 or 13 or 14 or 15 or 16)

20 (17 and 18 and 19)

21limit 20 to yr="2002 -Current"

EMBASE (Ovid)

1 exp fibrosing alveolitis/

2 exp interstitial pneumonia/

3 exp lung fibrosis /

4 (pulmonary adj3 fibros$).mp.

5 (interstitial adj3 pneumoni$).mp.

6 exp disease exacerbation /

7 exp deterioration /

8 (acute adj3 exacerbation?).mp.

9 (disease adj3 progression?).mp.

10 (disease adj3 exacerbation?).mp.

11 risk$.mp.

12 diagnos$.mp.

13 follow-up.mp.

14 ep.fs.

15 outcome.tw.

16 exp disease course/

17 (1 or 2 or 3 or 4 or 5)

18 (6 or 7 or 8 or 9 or 10)

19 (11 or 12 or 13 or 14 or 15 or 16)

20 (17 and 18 and 19)

21 limit 20 to yr="2002 -Current"

Science Citation Index Expanded (Web of Science)

#1 TS=("interstitial NEAR/3 lung NEAR/3 disease$") OR TS=("interstitial NEAR/3 pneumonia$") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*")

#2 TS=(acute NEAR/3 exacerbation$) OR TS=(disease NEAR/3 progression$) OR TS=(disease NEAR/3 exacerbation$) OR TS=(deterioration$)

#3 TS=(prognos*) OR TS=(mortality) OR TS=(outcome) OR TS=(course$) OR TS=(follow-up) OR TS=(predict*) OR TS=(incidence) OR TS=(risk)

#4 #1 AND #2 AND #3

#5 #4 AND (2002-2019)

Google scholar

("acute exacerbation" OR "disease progression" OR "disease exacerbation") ("interstitial lung disease" OR "usual interstitial pneumonia" OR "idiopathic pulmonary fibrosis") (prognosis OR mortality OR outcome)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 e-Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 8 e-Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-9 e-Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9 e-Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 10-11 e-Table 4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 10-11 e-Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

For more information, visit: **www.prisma-statement.org**.

Checklist items for Meta-analyses of Observational Studies in Epidemiology (MOOSE)	Reported on Page
Reporting of background should include	
• Problem definition	Page 4-5
• Hypothesis statement	Not described
• Description of study outcome(s)	Page 5
• Type of exposure or intervention used	Page 5
• Type of study designs used	Page 5
• Study population	Page 5
Reporting of search strategy should include	
• Qualifications of searchers (eg, librarians and investigators)	Page 6
• Search strategy, including time period included in the synthesis and keywords	Page 6 e-Appendix
• Effort to include all available studies, including contact with authors	Page 6
• Databases and registries searched	Page 6
• Search software used, name and version, including special features used (eg, explosion)	Not described
• Use of hand searching (eg, reference lists of obtained articles)	Page 6
• List of citations located and those excluded, including justification	e-Figure 1
• Method of addressing articles published in languages other than English	Page 5
• Method of handling abstracts and unpublished studies	Page 5
• Description of any contact with authors	Not described
Reporting of methods should include	
• Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Not described

• Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Not described
• Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Not described
• Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Not described
• Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 6
• Assessment of heterogeneity	Page 7
• Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 7
• Provision of appropriate tables and graphics	e-Figure 1 (study flow diagram)
Reporting of results should include	
• Graphic summarizing individual study estimates and overall estimate	e-Table 4, 5
• Table giving descriptive information for each study included	e-Table 1
• Results of sensitivity testing (eg, subgroup analysis)	Page 12
• Indication of statistical uncertainty of findings	Page 10-11 e-Table 4, 5
Reporting of discussion should include	
• Quantitative assessment of bias (eg, publication bias)	Not described
• Justification of exclusion (eg, exclusion of non-English-language citations)	Not described
• Assessment of quality of included studies	Page 14
Reporting of conclusions should include	
• Consideration of alternative explanations for observed results	Page 13-14
• Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 14

• Guidelines for future research	Page 14
• Disclosure of funding source	Page 15

From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

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A systematic review and meta-analysis of prognostic factors of acute exacerbation of idiopathic pulmonary fibrosis

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Title page

Title

A systematic review and meta-analysis of prognostic factors of acute exacerbation of idiopathic pulmonary fibrosis

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Word count

5024

Abstract

Objective

To clarify prognostic factors of acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF).

Design

A systematic review and meta-analysis.

Data sources

Medline, EMBASE and Science Citation Index Expanded were searched from 2002 through 1 March 2019.

Eligibility criteria for selecting studies

The review included primary studies addressing the association between the outcomes such as all-cause mortality of AE of IPF and its potential prognostic factors, which were designated as any clinical information related to the outcomes.

Data extraction and synthesis

Two reviewers extracted relevant data independently and assessed risk of bias. Univariate results were pooled using a random-effects model if at least three studies were available. Prognostic factors were determined based on significant and consistent results on both univariate and multivariate analyses in the majority of studies.

Results

Out of a total of 6763 articles retrieved, 37 were eligible and 31 potential prognostic factors for all-cause mortality were selected. Each study was subject to certain methodological shortcomings. The following five factors were statistically significant by a meta-analysis of univariate results, which was confirmed by multivariate analysis, i.e., Acute Physiology and Chronic Health Evaluation (APACHE) II score (hazard ratio (HR) 1.10, 1.01-1.19), partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio (odds ratios (ORs) 0.31 in one study and 0.99 in three studies), lactate dehydrogenase (LDH) (HRs 1.002, 1.003, 1.01 and 1.02), white blood cell

(WBC) count (OR 1.38, 1.04-1.83) and oxygen therapy before AE (HRs 3.68, 1.05-12.9 and 2.34, 1.04-5.28) (multivariate analysis, 95% confidence interval).

Conclusions

APACHE II score, PaO2/FiO2 ratio, LDH, WBC count and oxygen therapy before AE were deemed as prognostic factors of AE of IPF. Although there are some methodological limitations in this study, these findings are reliable due to consistent results by both univariate and multivariate analyses.

Registration

CRD 42018106172

Keywords

Idiopathic pulmonary fibrosis, acute exacerbation, prognosis, systematic review, meta-analysis

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis addressed the shortcoming in previous reports of prognostic factors of AE of IPF, which were composed of only small studies and thus may have generated spurious results.
- All primary studies were subject to certain methodological constraints, which undermined the quality of evidence derived from this review.
- An applicability of the findings may be limited because most of the reports constituting this review were derived from only one region.

Introduction

Interstitial pneumonia (IP) is a heterogeneous clinical entity, which is characterized by common pathological findings of fibrosis in the interstitium of pulmonary parenchyma.[1] Idiopathic pulmonary fibrosis (IPF) is the most common IP among idiopathic IPs (IIPs) with no apparent causes.[2] The disease has been at the centre of vigorous research over the last few decades given the evolution of diagnostic modalities.[3] IPF is known to be a fatal disease leading to respiratory failure due to its natural progression [4] and other comorbidities such as lung cancer, infection and cardiovascular diseases.[5] However, the most common cause of deaths of IPF is the event called an acute exacerbation (AE), occurring in approximately 40% of the cases.[6] This unique phenomenon was first reported as small case series, in which three patients with IPF presented with acute worsening of respiratory symptoms alongside with newly emerging bilateral radiological opacities that were related to no identifiable causes.[7] Subsequently, AE of IPF was recognized as not uncommon phenomenon and defined both clinically and radiologically by the latest international diagnostic criteria.[8] The pathogenesis of AE of IPF is still unknown although previous research disputed whether it is an autonomic acceleration of fibrotic process or an aggravation caused by external stimuli.[9] It is unpredictable in most cases regardless of some risk factors described by previous studies.[10] Once AE of IPF develops, the prognosis of this condition is extremely dismal due to no established therapeutic options.[11] However, there is a variation of mortality in previous reports, e.g., an estimated in-hospital mortality of 80% by an earlier study [12] and 90-day mortality of 70% by a recent study.[13] These discrepancies may suggest that the prognosis of AE of IPF varies between patients although between-study variations may be largely attributed to selection bias.[14] The knowledge of prognostic factors that would determine the prognosis of an individual patient is vital to make a therapeutic strategy, provide patients and families with relevant information to guide their decision-making and help design future research of pharmaceutical intervention.[15] Some research groups previously investigated prognostic factors of AE of IPF.[16] However, these previous findings may be anecdotal because most of them were derived from retrospective studies with a small sample size.[17] In addition, a prospective cohort study to investigate prognostic factors of AE of IPF may be unfeasible because of the unpredictable course of the disease, preventing recruitment of a larger sample size.[18] Therefore, the aim of this systematic review and meta-analysis was to overcome the limitation of a primary study in this research area and summarize current evidence

regarding prognostic factors of AE of IPF. This study was registered with International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018106172).

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[20] The methods were described briefly as the in-depths of methodology of this study were reported as a protocol paper beforehand.[21]

Patient and public involvement

There was no patient and public involvement in the whole process of conducting this research.

Eligibility criteria

Patients with AE of IPF were eligible for this review. AE and IPF were diagnosed based on previously published international guidelines relevant to respective condition or disease.[22-23] Subjects who presented with rapidly progressive IP at the first visit was included if radiological and/or pathological usual interstitial pneumonia (UIP) with no identifiable causes was confirmed. Only the first episode of AE was eligible if it was repeatedly manifested. The primary outcomes were short-term all-cause mortality and pulmonary-cause mortality, which were defined as in-hospital or 30-day mortality. The secondary outcomes were the proportion of patients discharged from the hospital and long-term all-cause mortality, which was determined at 90 days (3 months), 180 days (6 months) or 1 year after the diagnosis of the disease. Long-term health-related quality of life (hQOL) was also considered as the secondary outcome. All primary study types excluding case reports were considered for the review if quantitative data was available for any clinical information that had been investigated for their association with the outcomes. Editorials, letters, review articles and conference proceedings were not considered. Only research papers published in English in 2002 or later were reviewed as 2002 marked the year when the current classification system of IIPs was first introduced.[24]

Search strategy

Electronic databases, i.e., Medline (Ovid), EMBASE (Ovid) and Science Citation Index Expanded (Web of Science) were searched using subject headings and text words related to study population such as 'idiopathic pulmonary fibrosis' and 'acute exacerbation' (supplementary e-Appendix). The search was conducted on the 1st of March 2019. The reference lists of eligible studies and relevant review articles were also hand-searched to find additional reports. Grey literature was identified using Google Scholar.[25]

Study selection and data extraction

Two reviewers (H.K. and O.M.P.) independently examined titles and abstracts of all retrieved articles to identify eligible reports. Data was extracted based on a modified data extraction form, which was previously published in a protocol paper reviewing prognostic factors.[26] Extracted data included first author's name, year of publication, study location, study design, sample size, demographic features of subjects, outcomes, potential prognostic factors and their effect estimates, methods for statistical analysis and items associated with risk of bias. Any uncertainties or disagreements between reviewers arising from these processes were resolved through discussions. Authors were contacted to inquire about uncertain data or request for additional relevant information.

Potential prognostic factors

Any clinical information relevant to the pre-defined outcomes, which was reported by a minimum of three separate studies using either univariate or multivariate analysis, was further investigated as potential prognostic factors for this review. If the same research group reported a certain potential prognostic factor for a certain outcome in multiple studies, only the result derived from the study with the largest sample size was considered.

Risk of bias in individual studies

The Quality in Prognostic Studies (QUIPS) tool was applied to assess risk of bias in individual studies. Overall risk of bias was rated as previously reported.[27]

Statistical analysis

Summary statistics and statistical synthesis

The effect of potential prognostic factors was summarized with hazard ratios (HRs), odds ratios (ORs) or mean differences (MDs) depending on the types of available data. If an association between a potential prognostic factor and an outcome of interest was

presented using the same summary statistics in three or more studies, the results were statistically combined. Pooled results were summarized separately using HRs, ORs or MDs. If the unit of MD varied between studies, standardized MD (SMD) was calculated for meta-analysis.[28] Only unadjusted effect estimates of potential prognostic factors were combined and the effect estimates derived from multivariate models were described qualitatively. If meta-analysis was feasible from the collated data, it was conducted using a random-effects model employing the DerSimonian and Laird method.[29] Meta-analysis was conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All the results were presented with the 95% confidence interval (CI) if available and the 95% prediction interval (PI) was also calculated if the effect estimates were pooled and there was heterogeneity between studies.[30] Statistical significance was considered with a p-value of <0.05. If combining data was deemed inappropriate (due to a small number of studies or substantial clinical or methodological diversity between studies), the results were reported qualitatively.

Heterogeneity

Between-study variance was estimated using Tau^2 and assessed using both Q statistic and I^2. For the assessment of heterogeneity between studies, statistical significance was considered with a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity was categorised as mild (0 to 30%), moderate (30 to 50%), considerable (50 to 70%) and substantial (70 to 100%).[31] To better interpret sources of heterogeneity, a subgroup analysis was to be conducted based on the definition of AE of IPF (idiopathic or triggered),[8] study location (Asia or non-Asia) and sample sizes (N≤50 or N>50) if there was statistically significant heterogeneity. As mortality was defined at a varied point in time by each study, it was also considered in subgroup analysis. Sensitivity analysis was to be conducted focusing on studies with low risk of bias.

Small study bias

Small study bias such as publication bias was to be examined using graphical asymmetry of a funnel plot and the Egger's test,[32] if 10 or more studies were available for meta-analysis. A p-value of <0.1 was considered as statistical significance due to the low power of the test. If publication bias was suspected, an adjusted summary effect was to be estimated using the trim and fill method.[33]

Confirmation of prognostic factors

Prognostic factors were confirmed if their effects were in the same direction and statistically significant in the majority of studies by both univariate and multivariate analyses. If a meta-analysis was conducted, its pooled effect was assigned to each study constituting the analysis in assessing the number of significance and consistency of individual studies. In other words, the effect estimate of individual studies was overridden by the result of meta-analysis to calculate the number of significant and consistent studies.

Confidence in cumulative evidence

The credibility of evidence generated from this systematic review was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system, which was composed of five domains to rate down the quality of evidence (study limitation, inconsistency, indirectness, publication bias and imprecision) and two domains to rate it up (moderate/large effect size and dose response gradient). [34] The GRADE system was applied to the final list of confirmed prognostic factors generated from both univariate and multivariate results.

Results

Search strategy

A total of 6763 reports were identified through Medline, EMBASE, Science Citation Index Expanded and Google Scholar. After excluding 1368 duplicates, 79 non-English records, 3293 reports of ineligible study types (consisting of 1353 conference proceedings, 1068 review articles, 294 editorials or letters and 578 case reports) and 1917 articles that did not relate to the topic of interest, the remaining 106 reports were obtained as full-texts. Out of these, 69 reports were excluded due to no prognosis in 43 studies, IP other than IPF in 12 studies, deterioration other than acute exacerbation in 3 studies, an inclusion of stable IPF in 5 studies, multiple episodes of AE in one study and no quantitative data in 5 studies. Finally, 37 articles/studies [35-71] were eligible for this review (supplementary e-Figure 1, supplementary e-Table 1). No additional reports were identified from other potential sources.

Overview of included studies and potential prognostic factors

A total of 34 studies were conducted in Asia. Out of them the majority of studies took place in Japan (n=27), followed by Korea (n=6) and China (n=1). Two of the remaining 3 studies were conducted in Italy and the other one was in Greece. Thirty-three studies utilized a retrospective cohort design and the remaining one was a prospective cohort study. Twenty-four studies had a sample size of ≤50 participants and the other 13 studies had 51 to 100 participants, which yielded a total number of 1607 patients included in this review. The outcomes were all-cause mortality in 35 studies and disease-related mortality in 2 studies. The measure of hQOL was also described in one study. A total of 8 research groups conducted multiple studies using the same cohort and published reports (Collard 2010,[40] Kim 2006,[50] Lee 2012 [54] and Song 2011[62]; Kishaba 2018 [51] and Kishaba 2014 [52]; Enomoto 2015,[41] Enomoto 2018 [42] and Enomoto2019 [43]; Furuya 2017,[45] Isshiki 2015,[46] Koyama 2017 [53] and Sakamoto 2018 [59]; Nikaido 2018 [55] and Sand 2018 [60]; Kataoka 2015,[48] Suzuki 2018 [64] and Yokoyama 2010 [71]; Abe 2012 [35] and Atsumi 2018 [38]; Tomioka 2007 [66] and Yamazoe 2018 [70]) (supplementary e-Table 1). Among these multiple research conducted by the same groups the study with the largest sample size was prioritized and a total of 31 potential prognostic factors, which were investigated for their association with all-cause mortality, were identified and followed by further analysis (supplementary e-Table 2).

Risk of bias

The rate of attrition was not explicitly stated and this could have biased the results in the majority of the studies. There was also high risk of bias regarding confounding, statistical analysis and reporting in most of the studies. This was determined based on the finding that relevant potential confounders were not addressed or details regarding the models used for the analysis were insufficiently provided. Consequently, all studies were rated as being subject to some methodological flaws (supplementary e-Table 3).

Statistical analysis

Confirmation of prognostic factors

All potential prognostic factors were reported using univariate analysis in three or more studies. Meta-analysis was conducted for 17 out of the total of 31 potential prognostic factors. The effect estimates of the following 7 factors were in the same direction and statistically significant in the majority of the studies by univariate analysis. These

prognostic factors were as follows; Acute Physiology and Chronic Health Evaluation (APACHE) II score, extent of ground glass opacity (GGO) and consolidation on high resolution computed tomography (HRCT) scan, partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio, C-reactive protein (CRP), lactate dehydrogenase (LDH), white blood cell (WBC) and oxygen therapy before AE (supplementary e-Table 4). Out of the total of 31 potential prognostic factors, 20 were reported by multivariate analysis, mostly derived from a single or few studies. Among them, the effect estimates of 9 factors were in the same direction and statistically significant in the majority of the studies. These prognostic factors were as follows; APACHE II score, distribution pattern of newly emerging radiological opacities and extent of abnormality on HRCT scan, PaO2/FiO2 ratio, LDH, WBC, D-dimer, neutrophil in bronchoalveolar fluid (BAL), oxygen therapy before AE (supplementary e-Table 5). Based on the pre-defined criteria of prognostic factors that considered both univariate and multivariate analyses, 5 factors were confirmed as prognostic factors. The results of the other non-prognostic factors were described in a supplementary file (supplementary e-Table 4-5, supplementary e-Figure 2-20).

Effect of prognostic factors

A total of four studies reported APACHE II score using univariate analysis and the results of three studies were combined. Based on the combined result, APACHE II score was significantly associated with all-cause mortality of AE of IPF with an HR of 1.09 (95%CI: 1.04-1.15) (Figure 1). The remaining one study excluded from meta-analysis demonstrated a higher APACHE II score for non-survivors although it was not statistically significant (MD 2.80 (95%CI: -1.19-6.79) (Nikaido 2018 [55]) (supplementary e-Table 4). A multivariate analysis reported by one study demonstrated a significant result with an HR of 1.10 (95%CI: 1.01-1.19) (Kawamura 2017 [49]), which was consistent with the combined result of univariate analysis (supplementary e-Table 5).

A total of 15 studies reported PaO2/FiO2 ratio using univariate analysis. The results of six studies were combined using an HR while those of other three and four studies were combined using an OR and an MD, respectively. Based on the combined results, PaO2/FiO2 ratio was significantly associated with all-cause mortality of AE of IPF with an HR of 0.95 (95%CI: 0.92-0.97) (Figure 2) and an OR of 0.92 (95%CI: 0.89-0.95) (Figure 3). Another result of meta-analysis demonstrated a marginal significance with

an MD of -76.3 (95%CI: -153.9-1.28) (Figure 4). Of the remaining two studies excluded from meta-analysis, one study reported a non-significant lower PaO2/FiO2 ratio for non-survivors than survivors (195 vs. 240) (Novelli 2016 [56]) whereas the other study demonstrated a point estimate in the opposite direction from the other studies with no statistical significance (HR 1.45 (95%CI: 0.71-3.03)) (Sokai 2017 [62]) (supplementary e-Table 4). A total of five studies reported PaO2/FiO2 ratio using multivariate analysis. PaO2/FiO2 ratio was demonstrated to be significantly associated with all-cause mortality in four studies with ORs of 0.99 (95%CI: 0.98-1.00) (Kang 2018 [47]) and 0.99 (95%CI: 0.99-1.00) (Sakamoto 2018 [59]) and HRs of 0.99 (95%CI: 0.99-1.00) (Kishaba 2018 [51]) and 0.31 (95%CI: 0.14-0.67) (Suzuki 2018 [64]), respectively. In another study, the effect estimate was null value with no statistical significance (Yamazoe 2018 [70]). All of these results by multivariate analysis were consistent with the combined result of univariate analysis when the result with the same summary statistics was compared although one unit of PaO2/FiO2 ratio to calculate ORs and HRs were unclear in some studies (supplementary e-Table 5).

A total of 13 studies reported LDH using univariate analysis. The results of seven studies were combined using an HR while those of other four studies were combined using an SMD. Based on the combined results, LDH was significantly associated with all-cause mortality of AE of IPF with an HR of 1.02 (95%CI: 1.01-1.02) (Figure 5) and an SMD of 0.48 (0.11-0.84) (Figure 6), respectively. The remaining two studies excluded from meta-analysis demonstrated similar non-significant results with ORs of 1.02 (95%CI: 1.00-1.04) (Kang 2018 [47]) and 1.01 (95%CI: 1.00-1.01) (Sakamoto 2018 [59]) (supplementary e-Table 4). A total of five studies reported LDH using multivariate analysis. LDH was demonstrated to be significantly associated with all-cause mortality in four studies with HRs of 1.002 (95%CI: 1.000-1.004) (Akira 2008 [36]), 1.003 (95%CI: 1.001-1.005) (Kishaba 2018 [51]), 1.01 (95%CI: 1.00-1.01) (Enomoto 2018 [42]) and 1.02 (95%CI: 1.00-1.05) (Sokai 2017 [62]). The other one study demonstrated non-significant result with an OR of 1.00 (95%CI: 1.00-1.00)) (Kang 2018 [47]). All of these results by multivariate analysis were consistent with the combined result of univariate analysis when the result with the same summary statistics was compared although one unit of LDH to calculate HRs were unclear in some studies (supplementary e-Table 5).

A total of 10 studies reported WBC using univariate analysis and the results of six studies were combined. Based on the combined result, non-survivors demonstrated a

significantly higher value of WBC than survivors with an MD of 1.35 (95%CI: 0.19-2.51) (Figure 7). All of the remaining four studies excluded from meta-analysis demonstrated a point estimate of null value (supplementary e-Table 4). A multivariate analysis reported by one study demonstrated that WBC was significantly associated with all-cause mortality of AE of IPF with an OR of 1.38 (95%CI: 1.04-1.83) (Yamazoe 2018 [70]) (supplementary e-Table 5).

A total of four studies reported oxygen therapy before AE using univariate analysis and the results of all these studies were combined. Based on the combined result, oxygen therapy before AE was significantly associated with all-cause mortality of AE of IPF with an HR of 1.88 (95%CI: 1.15-3.09) (Figure 8). A multivariate analysis reported by two studies demonstrated that oxygen therapy before AE was significantly associated with all-cause mortality of AE of IPF with HRs of 3.68 (95%CI: 1.05-12.9) (Enomoto 2018 [42]) and 2.34 (95%CI: 1.04-5.28) (Sokai 2017 [62]). Both results by multivariate analysis were greater than the combined result of univariate analysis (supplementary e-Table 5).

Adjusted factors in multivariate analysis

A total of 13 studies conducted multivariate analysis. Adjusted factors were clearly described in six studies where two studies allowed one factor each (Enomoto 2018,[42] Kataoka 2015 [48]) while the other four studies allowed more than three factors, which included some of the following prognostic factors, i.e., PaO2/FiO2 ratio, LDH, WBC count and oxygen therapy before AE (Akira 2008,[36] Kishaba 2018,[51] Sokai 2017,[62] Yamazoe 2018 [70]). Overall, adjusted factors were diverse between studies (supplementary e-Table 4 and supplementary e-Table 5).

Additional analysis

There was substantial heterogeneity in the result of meta-analysis using an MD for PaO2/FiO2 ratio (chi^2=32.91, p<0.00001, I^2=91%) (Figure 4). There was no variability in the location of study, the number of participants and diagnostic criteria for AE. All studies were conducted in Japan and included 50 or fewer patients who were diagnosed by nearly the same criteria. However, the effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. Meta-analysis excluding this study generated a significant result with an MD of -117.7 (95%CI: -148.0--87.5) and no heterogeneity was identified (chi^2=1.69, p=0.43, I^2=0%) (supplementary e-Figure 21).

Two additional subgroup analyses were conducted for non-prognostic factors (the result was described in supplementary e-Figure 15, 17) but sensitivity analysis was not undertaken due to the small number of studies with low risk of bias. Small study bias including publication bias could not be assessed because the designated minimum number of studies (≥10) was not available for meta-analysis of any prognostic factor.

Quality of evidence

The starting point for the quality level of all of the evidence generated in this review was considered moderate because this review was phase 1 explanatory research to identify the association between the outcome and potential prognostic factors. In addition, study limitation was considered present in all of the evidence because no studies were rated as low risk of bias. Publication bias was also assumed to exist as this was a review for prognostic studies.[34] As a result, the GRADE system rated the quality of evidence for identified prognostic factors as either low or very low (supplementary e-Table 6).

Discussion

This systematic review and meta-analysis elucidated clinical information predictive of all-cause mortality of AE of IPF based on both univariate and multivariate analyses. These prognostic factors consisted of APACHE II score, PaO2/FiO2 ratio, LDH, WBC and oxygen therapy before AE. The effect of these factors exhibited by pooled analysis of univariate results was consistent with those derived from multivariate analysis except for oxygen therapy before AE, which displayed much greater effect by multivariate analysis. This finding will ensure the reliability of a confirmed list of prognostic factors and their effect estimates that were presented in this study. The knowledge of prognostic factors, which are composed of clinical information that is easily accessible in daily clinical practice, will be of great help in developing therapeutic strategies for this intractable disease and can be very informative to patients and families in facilitating their decision-making.

Among the identified prognostic factors, oxygen therapy before the development of AE suggests that the disease has already been in an advanced stage and there remains a limited capacity of the lung. The PaO2/FiO2 ratio reflects the extent of the damage to the pulmonary parenchyma and the severity of the disease. LDH is a ubiquitous molecule distributed over the body and increases in bloodstream after tissue

destruction.[72] Accordingly, a higher value of LDH may indicate extensive damage in the lung although LDH is not a specific marker for pulmonary disease. A non-specific inflammatory maker such as WBC elevates when the body is exposed to external stressful circumstances.[73] Therefore, an elevation of WBC may reflect the severity of the disease although it may possibly be an indicator of occult infection that could not be identified by ordinary diagnostic procedures. Acute physiologic scoring system such as APACHE II score is usually applied to in-patients in intensive care unit to assess the severity of their conditions. It is an established tool and known to correlate to the prognosis of a disease.[74] Although this system is composed of multiple factors that are not directly caused by the disease localized to the lung, such as renal dysfunction and electrolyte disturbance, the wide range of respiratory indexes is also included as its components. As a result, a higher value of APACHE II score may indicate respiratory distress caused by severely damaged pulmonary parenchyma.

Overall, all of these prognostic factors are indicating progressive or severe disease state. They are analogous to those of other IPs.[75-76] In particular, oxygenation at presentation is reported to be predictive of the prognosis of the disease.[18] However, pulmonary function was not deemed as a prognostic factor in this study. This difference may suggest that the severity of the insult at the onset of AE is more closely associated with the subsequent clinical course of the disease. On the other hand, pulmonary state before AE may foretell the development of this devastating condition.[77] There was also no association between radiological findings and all-cause mortality of AE of IPF in this review and this was inconsistent with the previous reports of other IPs.[75-76] In contrast to the implication of baseline pulmonary function, radiological findings at the development of AE may directly reflect the damaged area of pulmonary parenchyma. AE of IPs can be pathologically classified into diffuse alveolar damage (DAD), organizing pneumonia (OP) and fibroblastic foci.[78] The prognosis of AE is reported to be closely related to these pathological patterns. In short, DAD demonstrates the worst prognosis.[79] However, these pathological findings are not necessarily correlated to radiological findings.[80] This may account for the finding of this review that no radiological findings were deemed as prognostic of all-cause mortality of AE of IPF. Previous studies demonstrated that mechanical procedures such as surgery and radiation [81-82] and the presence of pulmonary hypertension [83-84] can be a risk factor for the development of AE of IPF. However, these factors were not identified as a prognostic factor in this review. Although mechanical procedures would be related to the prognosis of IPF rather than AE of IPF, proper safety precautions, such as risk stratification by

baseline pulmonary function should be taken beforehand to prevent the development of the disease.[81-82] The finding that pulmonary hypertension was not identified as a prognostic factor of AE of IPF may be explained by the speculation that it may not necessarily be related to the severity of the insult causing AE, which seems to be directly associated with the prognosis of this condition.

The methodology of this review may have affected the selection and confirmation of prognostic factors although it had been reported in a protocol paper beforehand.[21] Potential prognostic factors were defined as any clinical information reported in three or more studies assuming that frequent reports would likely imply clinical relevance. However, this arbitrary definition may have missed other potential prognostic factors. In addition, prognostic factors were confirmed by the results of both univariate and multivariate analyses based on statistical significance and the effect estimates in the same direction in the majority of included studies. It is possible that univariate results of prognostic factors that were confirmed in this review were confounded each other or by other factors in individual studies. For example, serum makers such as LDH and WBC may have been influenced by PaO2/FiO2 ratio, which may directly reflect the severity of the aggression. APACHE II score may also have been confounded by PaO2/FiO2 ratio because the latter is a component of the former index. Similarly, PaO2/FiO2 ratio may have been confounded by the extent of radiological abnormalities. Oxygen therapy before AE may have been reflecting impaired pulmonary function at baseline. However, at least on a study level, these potential confounding effects were not considered too serious to conduct meta-analysis because there was no concerning heterogeneity between studies except for PaO2/FiO2 ratio summarized by an MD. Although it was desirable to investigate the effect of other factors on combined univariate results, a further analysis such as meta-regression was not conducted due to a small number of studies. However, the effect of confirmed prognostic factors revealed by pooled analysis of univariate results was consistent with those derived from multivariate analysis. Therefore, the effect estimates by meta-analysis of univariate results do not seem to be unreliable although the result of multivariate analysis should also be interpreted with caution. Multivariate analysis was conducted in a total of 13 studies. Of these, adjusted factors were clearly described in only six studies where only a single confounder with less relevance was adjusted in two studies each and adjusted factors were diverse in the other four studies. Furthermore, the results of multivariate analysis for all potential prognostic factors except for two were derived from only a single or few studies. As a result, a confirmation of prognostic factors was influenced by the results of this small

number of studies, which may have turned out to be statistically significant by chance or non-significant due to low statistical power. These are the major methodological limitations of this review.

There is also some caveat that needs to be kept in mind to interpret the findings of this review. First, each study included in this review reported all-cause mortality at an arbitrary point in time such as in-hospital, 30 days, 90 days and overall. However, subgroup analysis was limited due to a small number of studies included for meta-analysis. Instead, causative clinical and/or methodological differences were sought to be identified qualitatively if there was statistically significant heterogeneity between studies. Second, most of the studies in this review were conducted in Japan. This finding may be related to the fact that AE of IPF was first reported by Japanese research group [7] and subsequently investigated vigorously in Japan.[85] In addition, it is reported that Japanese patients would more frequently develop progressive IP secondary to other medical conditions such as connective tissue disease [86] and drug toxicity.[87] Therefore, it is possible that Japanese people may be genetically more susceptible to AE of IPF, which may have led to more reports from Japan although the incidence of AE was similar between ethnicities in a recent study.[88] This unbalanced report will limit an applicability of the findings of this review because they were mostly derived from data of Japanese patients. Third, the quality of evidence of this review was deemed low or very low for all prognostic factors by the GRADE system. This is mostly because of methodological shortcomings in all studies where many potential confounders were not addressed or details were insufficiently provided regarding the models used for the analysis. This may also be related to the fact that all included studies were of retrospective design with a small sample size conducted in a single medical institution. Therefore, further research of high quality, in particular, a prospective cohort study involving multi-institutions in different countries, is imperative to make a definitive conclusion. Finally, other clinical information that was not addressed in this review may have the potential as a prognostic factor for AE of IPF. For example, increased monocyte count has recently been presented as a cellular biomarker for poor prognosis of IPF.[89] Future studies should investigate their role in AE of IPF.

Conclusion

This systematic review and meta-analysis demonstrated that APACHE II score, PaO2/FiO2 ratio, LDH, WBC count and oxygen therapy before AE were deemed as

prognostic factors of AE of IPF. Although there are some methodological limitations in this study, these findings are reliable due to consistent results by both univariate and multivariate analyses.

Ethics approval and participant consent

Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Data sharing

The dataset used and/or analyzed for this review will be available from the corresponding author upon a reasonable request and may become open to the public through a digital repository (such as Dryad) after the final result is published in a journal.

Conflict of interest

None to declare.

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Authors' contributions

H.K. planned the entire research project and analysed the data. He also summarized the result and wrote the manuscript. H.K. has full access to the data and takes responsibility for its integrity as well as the accuracy of the analysis.

O.M.P. contributed to the design of the research project and conducted the literature search and data extraction. He was also involved in revising the manuscript.

All researchers provided thoughts and opinions to compile a draft paper with revisions and then approved of the final version of the manuscript.

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Figure legends

Figure 1. Forrest plot of the result of univariate analysis for APACHE II score

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 194 patients were included. APACHE II score was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.09 (95% confidence interval: 1.04 to 1.15, p=0.0009). There was no heterogeneity (chi^2=0.95, p=0.62, I^2=0%).

Figure 2. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio (combined by hazard ratio)

The result of univariate analysis in 6 studies were pooled for meta-analysis and a total of 325 patients were included. PaO2/FiO2 ratio was significantly associated with all-cause mortality with a hazard ratio (HR) of 0.95 (95% confidence interval: 0.92 to 0.97, p<0.0001). There was no heterogeneity (chi^2=4.66, p=0.46, I^2=0%).

Figure 3. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio (combined by odds ratio)

The result of univariate analysis in 3 studies were pooled for meta-analysis and a total of 236 patients were included. PaO2/FiO2 ratio was significantly associated with all-cause mortality with an odds ratio (OR) of 0.92 (95% confidence interval: 0.89 to 0.95, p<0.00001). There was mild heterogeneity with no statistical significance (chi^2=2.46, p=0.29, I^2=19%). The 95% prediction interval ranged from 0.75 to 1.13.

Figure 4. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen/ fraction of inspired oxygen (PaO2/FiO2) ratio (combined by mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. There was no significant difference of PaO2/FiO2 ratio between non-survivors and survivors with a mean difference (MD) of -76.3 mmHg (95% confidence interval: -153.9 to 1.28, p=0.05). There was substantial heterogeneity with statistical significance (chi^2=32.91, p<0.00001, I^2=91%). The 95% prediction interval ranged from -435.2 to 282.6. All studies were conducted in Japan and implemented nearly the same definition of AE of IPF. The number of included patients were 50 or fewer in all studies. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. It analysed 28-day all-cause mortality whereas the other three studies analysed either in-hospital, 60-day or overall all-cause mortality.

Figure 5. Forrest plot of the result of univariate analysis for lactate dehydrogenase (LDH) (combined by hazard ratio)

The result of univariate analysis in 7 studies was pooled for meta-analysis and a total of 425 patients were included. LDH was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.01 to 1.02, p<0.00001). There was no heterogeneity (chi^2=5.58, p=0.47, I^2=0%).

Figure 6. Forrest plot of the result of univariate analysis for lactate dehydrogenase (LDH) (combined by standardized mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. LDH was significantly associated with all-cause mortality with a standardized mean difference (SMD) of 0.48 (95% confidence interval: 0.11 to 0.84, p=0.01). There was no heterogeneity (chi^2=0.66, p=0.88, I^2=0%).

Figure 7. Forrest plot of the result of univariate analysis for white blood cell (WBC) count

The result of univariate analysis in 6 studies was pooled for meta-analysis and a total of 242 patients were included. WBC count was significantly associated with all-cause mortality with a mean difference (MD) of 1.35 (95% confidence interval: 0.19 to 2.51, p=0.02). There was mild heterogeneity with no statistical significance (chi^2=6.41, p=0.27, I^2=22%). The 95% prediction interval ranged from -1.15 to 3.85.

Figure 8. Forrest plot of the result of univariate analysis for oxygen therapy before acute exacerbation

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 160 patients were included. Oxygen therapy before acute exacerbation was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.88 (95% confidence interval: 1.15 to 3.09, p=0.01). There was no heterogeneity (chi^2=2.05, p=0.56, I^2=0%).

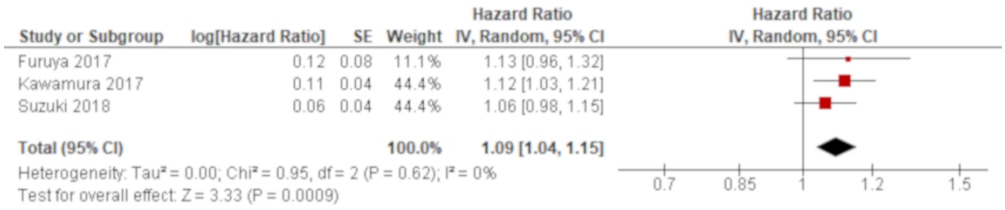


Figure 1

226x50mm (1400 x 1400 DPI)

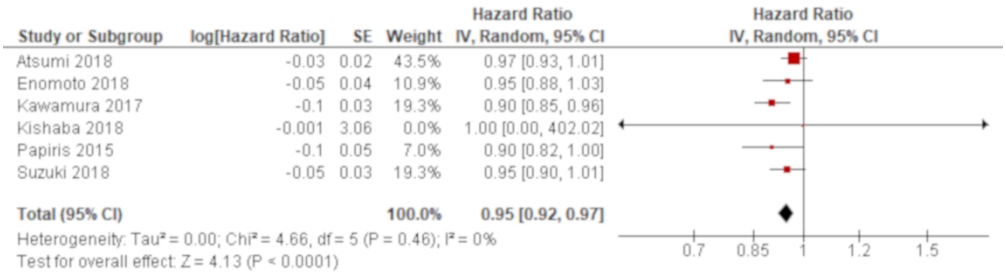


Figure 2

173x50mm (1600 x 1600 DPI)

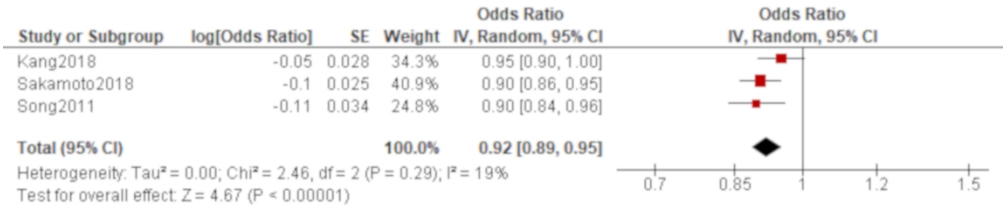


Figure 3

225x50mm (1400 x 1400 DPI)

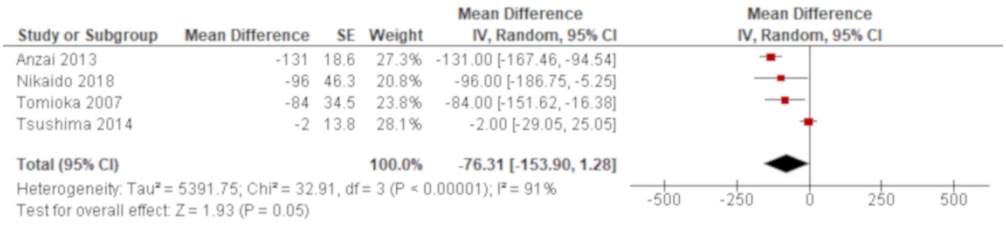


Figure 4

213x50mm (1400 x 1400 DPI)

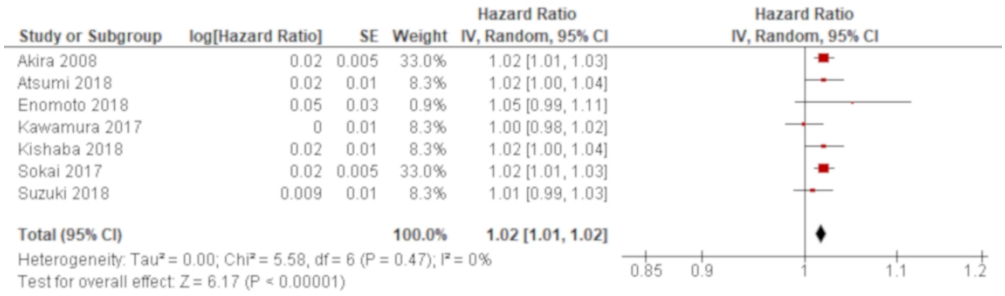


Figure 5

163x50mm (1600 x 1600 DPI)

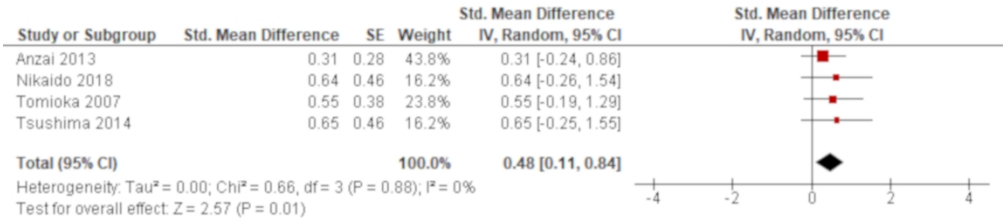


Figure 6

216x50mm (1400 x 1400 DPI)

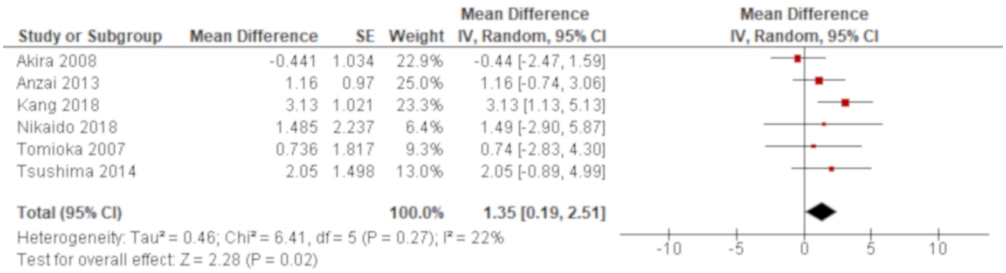


Figure 7

174x50mm (1600 x 1600 DPI)

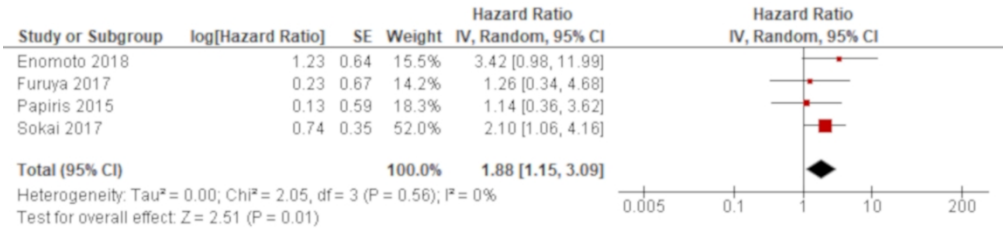


Figure 8

207x50mm (1450 x 1450 DPI)

Supplementary e-Table 1 Characteristics of 37 studies included for the review

Study	Country	Study design	Patients (n) (M/F)	Age (years)[a]	Smoking (n (%))	Follow-up lengths	Outcome	Number of deaths (%)[b]
Abe 2012 [35]	Japan	Retrospective cohort	73 (58/15)	67.5±8.2	Mean 937 (SD 658) (Smoking index)	-	All-cause mortality (3-month)	48 (65.8)
Akira 2008 [36]	Japan	Retrospective cohort	58 (44/14)	Median 66 (Range 45-82)	43 (74.1)	-	All-cause mortality (In-hospital)	25 (43.1)
Anzai 2013 [37]	Japan	Retrospective cohort	50 (41/9)	71.0±7.1[c]	(74.0)	-	All-cause mortality (Overall)	29 (58.0)
Atsumi 2018 [38]	Japan	Retrospective cohort	59 (49/10)	Median 74 (IQR 66-78)	Median 800 (IQR 500-1200) (Brinkman index)	-	All-cause mortality (60-day)	54 (91.5)
Cao 2016 [39]	China	Retrospective cohort	30 (23/7)	65.0±9.4	9 (30.0)	-	All-cause mortality (Overall)	26 (86.7)
Collard 2010 [40]	Korea	Retrospective cohort	47 (36/11)	66.0±8.0	40 (85.1)	-	All-cause mortality (Overall)	24 (51.1)
Enomoto 2015 [41]	Japan	Retrospective cohort	31 (28/3)	Median 69 (Range 50-84)	27 (87.1)	Median 53 months (Range 2-205)	All-cause mortality (3-month/12-month)	12 (38.7) (3 months) 23 (74.2) (12 months)
Enomoto 2018 [42]	Japan	Retrospective cohort	37	-	-	-	All-cause mortality (3-month)	10 (27.0)
Enomoto 2019 [43]	Japan	Retrospective cohort	37	-	-	-	All-cause mortality (3-month)	7 (18.9)
Fujimoto 2012 [44]	Japan	Retrospective cohort	60 (49/11)	Median 71 (IQR 63-75)	48 (80.0)	Median 370 days (Range 39-1230)	Disease-related mortality (Overall)	48 (80.0)

Furuya 2017 [45]	Japan	Retrospective cohort	47 (42/5)	Range 64-84	-	Median 173 days (Range 4-1137)	All-cause mortality (Overall)	27 (57.4)
Isshiki 2015 [46]	Japan	Retrospective cohort	41 (36/5)	72.6±6.4	36 (87.8)	Median 12 months (Range 1-143)	All-cause mortality (Overall)	29 (70.7)
Kang 2018 [47]	Korea	Retrospective cohort	66 (36/30)	70.8±9.0[c]	30 (45.5)	-	All-cause mortality (In-hospital)	29 (43.9)
Kataoka 2015 [48]	Japan	Retrospective cohort	40 (36/4)	Mean 72 (IQR 66-78)	-	-	All-cause mortality (3-month)	19 (47.5)
Kawamura 2017 [49]	Japan	Retrospective cohort	85 (66/19)	Median 76 (IQR 70-80)	-	-	All-cause mortality (60-day)	43 (50.6)
Kim 2006 [50]	Korea	Retrospective cohort	11	63.4±6.3 (n=8)	6 (75.0) (n=8)	-	All-cause mortality (In-hospital)	7 (63.6)
Kishaba 2018 [51]	Japan	Retrospective cohort	65 (40/25)	74.7±11.3	37 (56.9)	-	All-cause mortality (3-month)	-
Kishaba 2014 [52]	Japan	Retrospective cohort	58 (38/20)	75.0±9.6	58 (100.0)	Median 10.2 months (Range 0.1-112)	All-cause mortality (3-month)	- (70.7)
Koyama 2017 [53]	Japan	Retrospective cohort	47 (42/5)	Median 74 (Range 58-86)	42 (89.4)	-	All-cause mortality (3-month) Quality of life	19 (40.4)
Lee 2012 [54]	Korea	Retrospective cohort	24 (19/5)	64.3±9.4[c]	19 (79.2)	Median 74 days (IQR15-492)	All-cause mortality (Overall)	20 (83.3)
Nikaido 2018 [55]	Japan	Retrospective cohort	21 (21/0)	69.7±6.7[c]	-	-	All-cause mortality (60-day)	7 (33.3)

Novelli 2016 [56]	Italy	Retrospective cohort	11 (7/4)	Median 65 (IQR 55-75)	8 (72.7)	Median 18 months	All-cause mortality (3-month)	- (27.0)
Oishi 2016 [57]	Japan	Retrospective cohort	50 (46/4)	71.7±6.1	42 (84.0)	Median 42 days (Range 1-1656)	Disease-related mortality (Overall)	38 (76.0)
Papiris 2015 [58]	Greece	Retrospective cohort	17	-	-	-	All-cause mortality (Overall)	11 (39.3)
Sakamoto 2018 [59]	Japan	Retrospective cohort	80 (68/12)	72.9±6.3	67 (83.8)	Median 13 months (Range 1-137)	All-cause mortality (3-month)	- (46.3)
Sand 2018 [60]	Japan	Retrospective cohort	28 (28/0)	71.0±7.0	23 (82.1)	-	All-cause mortality (Overall)	13 (46.4) (at 100 days)
Saraya 2018 [61]	Japan	Retrospective cohort	27 (18/9)	Median 74 (IQR 70-84)	16 (66.7) (n=24)	-	All-cause mortality (60-day)	8 (29.6)
Sokai 2017 [62]	Japan	Retrospective cohort	59 (54/5)	71.7±8.2	49 (83.1)	-	All-cause mortality (180-day)	- (59.2)
Song 2011 [63]	Korea	Retrospective cohort	90 (69/21)	65.3±7.9	59 (65.6)	-	All-cause mortality (In-hospital)	45 (50.0)
Suzuki 2018 [64]	Japan	Retrospective cohort	62 (56/6)	Median 71 (IQR 64.8-76)	50 (80.6)	-	All-cause mortality (90-day)	32 (51.6)
Takei 2017 [65]	Japan	Retrospective cohort	18	-	-	-	All-cause mortality (90-day/Overall)	-
Tomioka 2007 [66]	Japan	Retrospective cohort	27 (18/9)	Mean 71 (Range 60-85)	20 (74.1)	-	All-cause mortality (In-hospital)	15 (55.6)
Tsushima 2014	Japan	Retrospective	20 (14/6)	76.8±1.9[c]	-	-	All-cause mortality	7 (35.0)

[67]		cohort					(28-day)	
Vianello 2019	Italy	Retrospective	20 (15/5)	67.0±10.4[c]	9 (45.0)	Maximum 370 days	All-cause mortality	10 (50.0)
[68]		cohort					(In-ICU /Overall)	(In-ICU)
Woottoon 2011	Korea	Prospective	43 (88%/12%)	Mean 65	(84.0)	-	All-cause mortality	- (51.2)
[69]		cohort					(60-day/Overall)	(60 days)
Yamazoe 2018	Japan	Retrospective	57		-	-	All-cause mortality	35 (61.4)
[70]		cohort					(In-hospital/Overall)	(In-hospital)
Yokoyama 2010	Japan	Retrospective	11 (7/4)	72.3±7.7	8 (72.7)	-	All-cause mortality	6 (54.5)
[71]		cohort					(3-month)	

a, indicates mean±standard deviation unless otherwise specified; b, indicates the number of deaths at each point in time unless otherwise specified; c, calculated using the sample size and median, range or interquartile range in two comparative groups;

IQR, interquartile range;

Supplementary e-Table 2 31 potential prognostic factors for all-cause mortality

Demographic characteristics
age, sex, smoking history, BMI, disease duration
Disease severity (staging) of underling IPF or acute phase
GAP system, JRS classification, APACHE II score
Symptoms (at onset)
Duration of dyspnoea, fever
Pulmonary function tests (at baseline)
FVC, DLCO, FEV1
Radiological features (at onset)
Pattern of distribution, GGO, reticular opacity, extent of GGO and consolidation, extent of abnormality
Laboratory findings (at onset)
PaO2/FiO2 ratio, CRP, LDH, KL-6, SP-D, WBC, D-dimer, FDP, BAL lymphocyte, BAL neutrophil
Treatment before acute exacerbation
Pirfenidone, corticosteroid, oxygen therapy

APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; BMI, body mass index; CRP, C-reactive protein; DLCO, diffusion capacity of the lung for carbon monoxide; FDP, fibrin degradation product; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; HR, hazard ratio; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO2/FiO2, partial pressure of arterial oxygen/fraction of inspired oxygen; SP-D, surfactant protein-D; WBC, white blood cell;

Supplementary e-Table 3 Risk of bias in 37 studies included for the review, assessed by the Quality in Prognostic Studies tool[a]

Study	study participation	study attrition	prognostic factor measurement	outcome measurement	study confounding	statistical analysis and reporting
Abe 2012 [35]	**high risk**	**high risk**	**high risk**	low risk	**high risk**	**high risk**
Akira 2008 [36]	medium risk	low risk	low risk	low risk	medium risk	**high risk**
Anzai 2013 [37]	low risk	low risk	medium risk	low risk	medium risk	**high risk**
Atsumi 2018 [38]	low risk	low risk	low risk	low risk	medium risk	**high risk**
Cao 2016 [39]	medium risk	low risk	low risk	low risk	**high risk**	**high risk**
Collard 2010 [40]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Enomoto 2015 [41]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Enomoto 2018 [42]	medium risk	**high risk**	low risk	low risk	medium risk	**high risk**
Enomoto 2019 [43]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Fujimoto 2012 [44]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Furuya 2017 [45]	low risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Isshiki 2015 [46]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Kang 2018 [47]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Kataoka 2015 [48]	low risk	**high risk**	medium risk	low risk	**high risk**	medium risk
Kawamura 2017 [49]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Kim 2006 [50]	medium risk	**high risk**	**high risk**	low risk	medium risk	**high risk**
Kishaba 2018 [51]	low risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Kishaba 2014 [52]	medium risk	**high risk**	medium risk	low risk	medium risk	**high risk**
Koyama 2017 [53]	low risk	low risk	medium risk	low risk	**high risk**	**high risk**

Lee 2012 [54]	low risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Nikaido 2018 [55]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Novelli 2016 [56]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Oishi 2016 [57]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Papiris 2015 [58]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Sakamoto 2018 [59]	low risk	**high risk**	low risk	low risk	medium risk	**high risk**
Sand 2018 [60]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Saraya 2018 [61]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Sokai 2017 [62]	low risk	**high risk**	low risk	low risk	medium risk	medium risk
Song 2011 [63]	medium risk	low risk	medium risk	low risk	**high risk**	**high risk**
Suzuki 2018 [64]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Takei 2017 [65]	medium risk	**high risk**	low risk	low risk	**high risk**	**high risk**
Tomioka 2007 [66]	low risk	low risk	low risk	low risk	**high risk**	**high risk**
Tsushima 2014 [67]	medium risk	low risk	low risk	low risk	**high risk**	**high risk**
Vianello 2019 [68]	**high risk**	**high risk**	low risk	low risk	**high risk**	**high risk**
Woottoon 2011 [69]	medium risk	**high risk**	medium risk	low risk	**high risk**	**high risk**
Yamazoe 2018 [70]	low risk	**high risk**	low risk	low risk	**high risk**	medium risk
Yokoyama 2010 [71]	medium risk	low risk	**high risk**	low risk	**high risk**	**high risk**

a, Text in bold refers to high risk of bias.

Supplementary e-Table 4 The result of univariate analysis of potential prognostic factors for all-cause mortality

Potential prognostic factors[a]	Analysis	Studies (n)[b]	Subjects (n)	Point estimate (+/-)[c]	Result of meta-analysis and non-pooled studies (95% CI)[d]
Demographic features					
Age	Meta	8	405	4/2	HR 1.00 (0.98-1.02) (/1 year)
		3	236	3/0	OR 1.02 (0.98-1.05) (/1 year)
	Not pooled	Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.83) (year)
		Anzai 2013 [37]	50	1/0	MD 3.50 (-0.48-7.48) (year) (non-survivor vs. survivor)
		Tsushima 2014 [67]	20	0/1	***MD -4.30 (-6.04--2.56) (yaer) (non-survivor vs. survivor)***
Sex	Meta	7	377	3/4	HR 0.93 (0.65-1.34) (vs. female)
		5	306	3/2	OR 1.28 (0.74-2.21) (vs. female)
	Not pooled	Kishaba 2014 [52]	58	0/1	HR 0.90 (p=0.76)
Smoking history	Meta	3	145	2/1	HR 0.98 (0.35-2.75) (vs. never-smoker)
		4	243	3/1	OR 0.99 (0.59-1.67) (vs. never-smoker)
		3	116	1/1	HR 1.00 (0.89-1.11) (/10 pack-year)
	Not pooled	Atsumi 2018 [38]	59	0/1	HR 0.95 (0.88-1.02) (/200 Brinkman index)
		Kishaba 2014 [52]	58	1/0	***HR 1.01 (p=0.03) (pack-year)***
BMI	Not pooled	Kang 2018 [47]	66	0/1	MD -0.13 (-2.12-1.86) (non-survivor vs. survivor)
		Suzuki 2018 [64]	62	1/0	HR 1.04 (0.94-1.15) (/1 kg/m^2)
		Lee 2012 [54]	24	0/1	HR 0.93 (0.82-1.05)
Disease duration before AE	Not pooled	Papiris 2015 [58]	17	1/0	HR 1.01 (1.00-1.03)
		Enomoto 2019 [43]	37	-/-	HR 1.00 (p=0.82) (/1 month)
		Song 2011 [63]	90	0/1	OR 0.99 (0.98-1.01) (months)

		Akira 2008 [36]	58	1/0	MD 2.00 (-11.6-15.6) (months) (non-survivor vs. survivor)
		Novelli 2016 [56]	11	0/1	8 vs. 20 (months) (non-survivor vs. survivor)
Disease severity (staging) of underling IPF or acute phase					
GAP system[e]	Not pooled	Atsumi 2018 [38]	59	1/0	***HR 1.45 (1.10-1.93) (/1 point)***
		Enomoto 2018 [42]	37	1/0	HR 1.08 (0.48-2.44) (/1 stage)
		Sakamoto 2018 [59]	80	1/0	OR 1.64 (0.98-2.70) (/1)
JRS classification[f]	Not pooled	Atsumi 2018 [38]	59	1/0	***HR 1.50 (1.17-1.94) (/1 stage)***
		Enomoto 2018 [42]	37	1/0	HR 2.12 (0.86-5.23)
		Sakamoto 2018 [59]	80	1/0	OR 1.28 (0.53-3.13) (advanced (III, IV))
APACHE II score	Meta	3	194	3/0	***HR 1.09 (1.04-1.15)(/1 point)***
	Not pooled	Nikaido 2018 [55]	21	1/0	MD 2.80 (-1.19-6.79) (non-survivor vs. survivor)
Symptoms					
Duration of dyspnoea	Not pooled	Song 2011 [63]	90	0/1	***OR 0.94 (0.90-0.98) (days)***
		Kishaba 2014 [52]	58	1/0	HR 1.01 (p=0.65) (days)
		Kang 2018 [47]	66	0/1	MD -6.43 (-15.9-3.04) (days) (non-survivor vs. survivor)
Fever	Meta	3	206	2/1	OR 1.66 (0.74-3.70)
	Not pooled	Enomoto 2019 [43]	37	0/1	HR 0.51 (p=0.39)
Pulmonary function					
FVC	Meta	5	199	1/3	HR 0.99 (0.98-1.01) (/1% predicted value)
		3	193	1/0	OR 1.01 (0.99-1.02) (/1% predicted value)
DLCO	Meta	4	171	1/2	HR 0.99 (0.98-1.01) (/1% predicted value)
	Not pooled	Kang 2018 [47]	66	0/1	MD -6.38 (-15.8-3.04) (% predicted value) (non-survivor vs. survivor)

		Sakamoto 2018 [59]	80	1/0	OR 1.01 (0.98-1.03)
FEV1	Not pooled	Kang 2018 [47]	66	0/1	MD -4.36 (-14.1-5.37) (% predicted value) (non-survivor vs. survivor)
		Koyama 2017 [53]	47	0/1	MD -11.0 (-23.8-1.82) (% predicted value) (non-survivor vs. survivor)
		Papiris 2015 [58]	17	-/-	HR 1.00 (0.94-1.06) (% predicted value)
Features on HRCT					
Pattern	Not pooled	Kim 2006 [50]	11	1/0	OR 30.3 (0.96-959.6) (multifocal vs. peripheral)
		Anzai 2013 [37]	50	1/0	OR 8.00 (0.82-78.0) (diffuse+multifocal vs. peripheral)
		Sakamoto 2018 [59]	80	1/0	OR 1.39 (0.55-3.45) (diffuse)
		Akira 2008 [36]	58	1/0	***HR 5.39 (2.60-11.2) (diffuse+multifocal vs. peripheral)***
		Kawamura 2017 [49]	85	0/1	HR 0.41 (0.10-1.71) (multifocal)
GGO	Not pooled	Sokai 2017 [62]	59	1/0	HR 1.01 (0.99-1.03)
		Papiris 2015 [58]	17	1/0	HR 1.65 (0.74-3.70)
		Lee 2012 [54]	24	1/0	HR 1.03 (1.00-1.06) (GGO score)
Reticular opacity	Not pooled	Akira 2008 [36]	58	1/0	HR 1.03 (1.00-1.06) (reticulation and honeycombing (%))
		Lee 2012 [54]	24	0/1	HR 0.96 (0.91-1.01) (reticulation score)
		Kishaba 2014 [52]	58	1/0	HR 1.32 (p=0.06) (traction bronchiectasis and honeycombing score)
		Sokai 2017 [62]	59	0/1	HR 0.98 (0.95-1.02) (reticulation and honeycombing (%))
Extent of GGO and	Not pooled	Kishaba 2014 [52]	58	1/0	***HR 1.85 (p=0.03) (score)***
consolidation		Akira 2008 [36]	58	1/0	***HR 1.05 (1.02-1.07) (%)***
		Sokai 2017 [62]	59	1/0	HR 1.02 (1.00-1.04) (%)
Extent of abnormality	Meta	3	120	3/0	HR 1.02 (1.00-1.05) (/1 score)
		Akira 2008 [36]	58	1/0	***HR 1.07 (1.04-1.10) (%)***

Laboratory findings					
PaO2/FiO2 ratio	Meta	6	325	0/5	***HR 0.95 (0.92-0.97) (/10 mmHg)***
		3	236	0/3	***OR 0.92 (0.89-0.95) (/10 mmHg)***
		4	118	0/4	MD -76.3 (-153.9-1.28) (non-survivor vs. survivor)
	Not pooled	Novelli 2016 [56]	11	0/1	195 vs. 240 (non-survivor vs. survivor)
		Sokai 2017 [62]	59	1/0	HR 1.45 (0.71-3.03) (≥200)
CRP	Meta	4	243	3/0	***HR 1.05 (1.02-1.08) (/1mg/dl)***
		6	242	7/0	***SMD 0.69 (0.19-1.18) (non-survivor vs. survivor)***
	Not pooled	Kishaba 2014 [52]	58	0/1	HR 0.98 (p=0.47) (mg/dl)
		Song 2011 [63]	90	1/0	***OR 1.09 (1.01-1.17) (mg/dl)***
		Sakamoto 2018 [59]	80	1/0	OR 1.05 (0.97-1.14) (mg/dl)
LDH	Meta	7	425	6/0	***HR 1.02 (1.01-1.02) (/10 IU/L)***
		4	118	4/0	***SMD 0.48 (0.11-0.84) (non-survivor vs. survivor)***
	Not pooled	Kang 2018 [47]	66	1/0	OR 1.02 (1.00-1.04)
		Sakamoto 2018 [59]	80	1/0	OR 1.01 (1.00-1.01) (IU/L)
KL-6	Meta	4	265	3/0	***HR 1.02 (1.01-1.04) (/100 U/mL)***
		4	118	2/2	MD -23.6 (-119.7-72.5) (×10 U/mL) (non-survivor vs. survivor)
	Not pooled	Kishaba 2014 [52]	58	1/0	***HR 2.01 (p=0.001) (IU/L)***
		Enomoto 2018 [42]	37	-/-	HR 1.00 (1.00-1.00) (U/mL)
		Collard 2010 [40]	47	0/1	OR 0.41 (0.06-2.93) (log unit)
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (1.00-1.00) (U/mL)
SP-D	Meta	4	243	0/2	HR 0.99 (0.99-1.00) (/10 ng/ml)
	Not pooled	Anzai 2013 [37]	50	1/0	MD 25.0 (-155.6-205.6) (non-survivor vs. survivor) (ng/ml)

		Nikaido 2018 [55]	21	1/0	MD 172.2 (-76.3-420.7) (non-survivor vs. survivor) (ng/ml)
		Collard 2010 [40]	47	1/0	OR 1.23 (0.36-4.21) (log ng/ml)
		Sakamoto 2018 [59]	80	1/0	OR 1.01 (1.00-1.01) (ng/ml)
WBC	Meta	6	242	5/1	***MD 1.35 (0.19-2.51) (×10^6/mm^3) (non-survivor vs. survivor)***
	Not pooled	Kataoka 2015 [48]	40	-/-	OR 1.00 (1.00-1.00) (/mm^3)
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (1.00-1.00) (/mm^3)
		Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.47) (/mm^3)
		Enomoto 2019 [43]	37	-/-	***HR 1.00 (p=0.03) (/ul)***
D-dimer	Not pooled	Suzuki 2018 [64]	62	1/0	***HR 1.03 (1.01-1.05) (/1 μg/ml)***
		Sakamoto 2018 [59]	80	0/1	OR 0.99 (0.94-1.04) (mg/ml)
		Nikaido 2018 [55]	21	1/0	MD 3.10 (-7.48-13.7) (μg/ml) (non-survivor vs. survivor)
FDP	Not pooled	Nikaido 2018 [55]	21	1/0	MD 3.0 (-21.6-27.6) (μg/ml) (non-survivor vs. survivor)
		Tsushima 2014 [67]	20	1/0	***MD 115.6 (73.5-157.7) (μg/ml) (non-survivor vs. survivor)***
		Sakamoto 2018 [59]	80	-/-	OR 1.00 (0.98-1.02) (μg/ml)
BAL lymphocyte	Not pooled	Song 2011 [63]	90	0/1	***OR 0.91 (0.83-0.99) (%)***
		Suzuki 2018 [64]	62	0/1	HR 0.97 (0.92-1.01) (/1%)
		Kishaba 2014 [52]	58	-/-	HR 1.00 (p=0.97)
BAL neutrophil	Not pooled	Song 2011 [63]	90	1/0	OR 1.06 (1.00-1.12) (%)
		Suzuki 2018 [64]	62	1/0	***HR 1.01 (1.00-1.03) (/1%)***
		Kishaba 2014 [52]	58	0/1	HR 0.94 (p=0.33)
Treatment before AE					
Pirfenidone	Meta	3	164	3/0	HR 1.34 (0.81-2.24)

		Sakamoto 2018 [59]	80	0/1	OR 0.85 (0.28-2.56)
Corticosteroid	Meta	3	161	2/1	HR 0.96 (0.61-1.52)
		Song 2011 [63]	90	0/1	OR 0.83 (0.35-1.94) (corticosteroid with or without cytotoxic agent)
		Sakamoto [59]	80	1/0	OR 1.75 (0.64-4.76)
Oxygen therapy	Meta	4	160	4/0	***HR 1.88 (1.15-3.09)***

a, Text in italic bold refers to potential prognostic factors, which demonstrated consistent and statistically significant results in the majority of studies. If the result of meta-analysis was significant, all studies included for the analysis were assumed to be significant to determine whether the majority of studies demonstrated significant results.

b, The number of included studies was described for meta-analysis while an individual study was specified for non-pooled studies.

c, Plus (+) indicates a positive association between mortality and potential prognostic factors based on point estimates while minus (-) indicates the negative association. Studies with null effects such as zero by MDs and one by HRs were not counted in this column. The direction of point estimates of all pooled and non-pooled studies were considered.

d, Parenthesis indicates 95% confidence interval unless otherwise specified. Text in bold refers to statistically significant results. Per unit for relative values such as ORs and HRs was described only if data was available and otherwise only unit was described.

e, The system considers gender, age and two lung physiology variables, i.e., FVC and DLCO. Points are assigned to each component of the system and there are three stages depending on the total points with a higher value indicating severer disease.

f, The classification consists of PaO_2 at rest and minimum SpO_2 during the six-minute walking test. There are four stages based on a combination of the value of both PaO2 and SpO2 with a higher stage indicating severer disease.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; BMI, body mass index; CRP, C-reactive protein; CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FDP, fibrin

degradation product; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; HR, hazard ratio; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; Meta, meta-analysis; OR, odds ratio; PaO_2, partial pressure of arterial oxygen; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio, SMD, standardized mean difference; SP-D, SpO2, saturation of percutaneous oxygen; surfactant protein-D; WBC, white blood cell;

Supplementary e-Table 5 The result of multivariate analysis of potential prognostic factors for all-cause mortality

Potential prognostic factors[a]	Studies (n)	Subjects (n)	Effect estimates (95% CI)[b]	Adjusted factors
Demographic features				
Age	Akira 2008 [36]	58	HR 1.00 (0.96-1.04) (year)	sex, smoking history, FVC, DLCO, pattern and extent of abnormality on HRCT, LDH
	Kang 2008 [47]	66	OR 0.97 (0.91-1.04) (year)	Unclear
	Yamazoe 2018 [70]	57	OR 0.96 (0.87-1.07) (year)	PaO2/FiO2 ratio, CRP, WBC, Hb, antibiotic therapy
Sex	Akira 2008 [36]	58	HR 0.91 (0.34-2.43) (vs. female)	age, smoking history, FVC, DLCO, pattern and extent of abnormality on HRCT, LDH
Smoking history	Akira 2008 [36]	58	HR 2.47 (0.91-6.70) (vs. never-smoker)	age, sex, FVC, DLCO, pattern and extent of abnormality on HRCT, LDH
	Sokai 2017 [62]	59	HR 0.51 (0.23-1.31)	GGO and consolidation, LDH, KL-6, oxygen therapy, asymmetrical exacerbation
Disease severity (staging) of underling IPF or acute phase				
GAP system[c]	Atsumi 2018 [38]	59	HR 0.98 (0.62-1.51) (/1 point)	Unclear
APACHE II score	Kawamura 2017 [49]	85	***HR 1.10 (1.01-1.19)***	Unclear
Symptoms				
Fever	Kang 2018 [47]	66	OR 1.35 (0.41-4.50)	Unclear
Pulmonary function				
FVC	Akira 2008 [36]	58	HR 0.98 (0.96-1.01) (% predicted value)	age, sex, smoking history, DLCO, pattern and extent of abnormality on HRCT, LDH
	Kang 2018 [47]	66	OR 1.00 (0.96-1.04) (% predicted value)	Unclear

DLCO	Akira 2008 [36]	58	HR 1.02 (1.00-1.04) (% predicted value)	age, sex, smoking history, FVC, pattern and extent of abnormality on HRCT, LDH
Features on HRCT				
Pattern	Akira 2008 [36]	58	***HR 4.63 (1.90-11.3)*** (diffuse+multifocal vs. peripheral)	age, sex, smoking history, FVC, DLCO, extent of abnormality on HRCT, LDH
Extent of GGO and consolidation	Kishaba 2014 [52]	58	***HR 2.29 (p=0.03)***	Unclear
	Akira 2008 [36]	58	HR 0.98 (0.95-1.02) (%)	Unclear
	Sokai 2017 [62]	59	HR 0.99 (0.96-1.02) (%)	smoking history, LDH, KL-6, oxygen therapy, asymmetrical exacerbation
Extent of abnormality	Akira 2008 [36]	58	***HR 1.07 (1.02-1.12) (%)***	age, sex, smoking history, FVC, DLCO, pattern of abnormality on HRCT, LDH
	Atsumi 2018 [38]	59	HR 1.18 (0.99-1.39) (/10 score)	Unclear
	Enomoto 2018 [42]	37	***HR 1.22 (1.01-1.48) (score)***	age
Laboratory findings				
PaO2/FiO2 ratio	Kang 2018 [47]	66	***OR 0.99 (0.98-1.00)***	Unclear
	Yamazoe 2018 [70]	57	OR 1.00 (0.99-1.01)	age, CRP, WBC, Hb, antibiotic therapy
	Kishaba 2018 [51]	65	***HR 0.99 (0.99-1.00)***	LDH, delta LDH, delta KL-6, criteria of AE
	Suzuki 2018 [64]	62	***HR 0.31 (0.14-0.67) (>300 vs. ≤300)***	Unclear
	Sakamoto 2018 [59]	80	***OR 0.99 (0.99-1.00)***	Unclear
CRP	Song 2011 [63]	90	***OR 2.47 (1.03-5.91) (mg/dl)***	Unclear
	Yamazoe 2018 [70]	57	OR 1.00 (0.90-1.13) (mg/dl)	age, PaO2/FiO2 ratio, WBC, Hb, antibiotic therapy

	Kataoka 2015 [48]	40	OR 1.18 (1.00-1.39) (mg/dl)	respiratory rate
LDH	Kang 2018 [47]	66	OR 1.00 (1.00-1.00)	Unclear
	Akira 2008 [36]	58	***HR 1.002 (1.000-1.004)***	age, sex, smoking history, FVC, DLCO, pattern and extent of abnormality on HRCT
	Kishaba 2018 [51]	65	***HR 1.003 (1.001-1.005) (IU/L)***	PaO2/FiO2 ratio, delta LDH, delta KL-6, criteria of AE
	Enomoto 2018 [42]	37	***HR 1.01 (1.00-1.01) (IU/L)***	age
	Sokai 2017 [62]	59	***HR 1.02 (1.00-1.05) (/10IU/L)***	smoking history, GGO and consolidation, KL-6, oxygen therapy, asymmetrical exacerbation
KL-6	Suzuki 2018 [64]	62	***HR 1.24 (1.05-1.46) (/500U/mL)***	Unclear
	Sokai 2017 [62]	59	HR 0.99 (0.96-1.02) (/100U/mL)	smoking history, GGO and consolidation, LDH, oxygen therapy, asymmetrical exacerbation
WBC	Yamazoe 2018 [70]	57	***OR 1.38 (1.04-1.83) (/μl)***	age, PaO2/FiO2 ratio, CRP, Hb, antibiotic therapy
D-dimer	Suzuki 2018 [64]	62	***HR 1.04 (1.02-1.06) (/1/μg/mL)***	Unclear
BAL lymphocyte	Song 2011 [63]	90	OR 0.87 (0.74-1.02) (%)	Unclear
BAL neutrophil	Suzuki 2018 [64]	62	***HR 1.02 (1.00-1.03) (%)***	Unclear
Treatment before AE				
Oxygen therapy	Enomoto 2018 [42]	37	***HR 3.68 (1.05-12.9)***	age
	Sokai 2017 [62]	59	***HR 2.34 (1.04-5.28)***	smoking history, GGO and consolidation, LDH, asymmetrical exacerbation

a, Text in italic bold refers to potential prognostic factors, which demonstrated consistent and statistically significant results in the majority of studies.

b, Parenthesis indicates 95% confidence interval unless otherwise specified. Text in bold refers to statistically significant results. Per unit for relative values such as ORs and HRs was described only if data was available and otherwise only unit was described.

c, The system considers gender, age and two lung physiology variables, i.e., FVC and DLCO. Points are assigned to each component of the system and there are three stages depending on the total points with a higher value indicating severer disease.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; CRP, C-reactive protein; CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GAP, gender, age and physiology; GGO, ground glass opacity; Hb, haemoglobin; HR, hazard ratio; HRCT, high resolution computed tomography; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; OR, odds ratio; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen, WBC, white blood cell

Supplementary e-Table 6 Assessment of quality of evidence of prognostic factors by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Outcome: all-cause mortality										
			GRADE factors							
Prognostic factors[a]	Analysis[b]	Phase	Study limitations	Inconsistency[c]	Indirectness	Publication bias	Imprecision	Moderate/large effect size	Dose response gradient	Overall quality
APACHE II score	Uni	1	+	-	-	+	-	-	-	Very Low
	Multi	1	+	N/A	-	+	-	-	-	Very low
PaO2/FiO2 ratio	Uni	1	+	-	-	+	-	+	-	Low
	Multi	1	+	-	-	+	-	-	-	Very low
LDH	Uni	1	+	-	-	+	-	-	-	Very low
	Multi	1	+	-	-	+	-	-	-	Very low
WBC	Uni	1	+	-	-	+	-	-	-	Very low
	Multi	1	+	N/A	-	+	-	-	-	Very low
Oxygen therapy	Uni	1	+	-	-	+	-	-	-	Very low
(before AE)	Multi	1	+	-	-	+	+	+	-	Very low

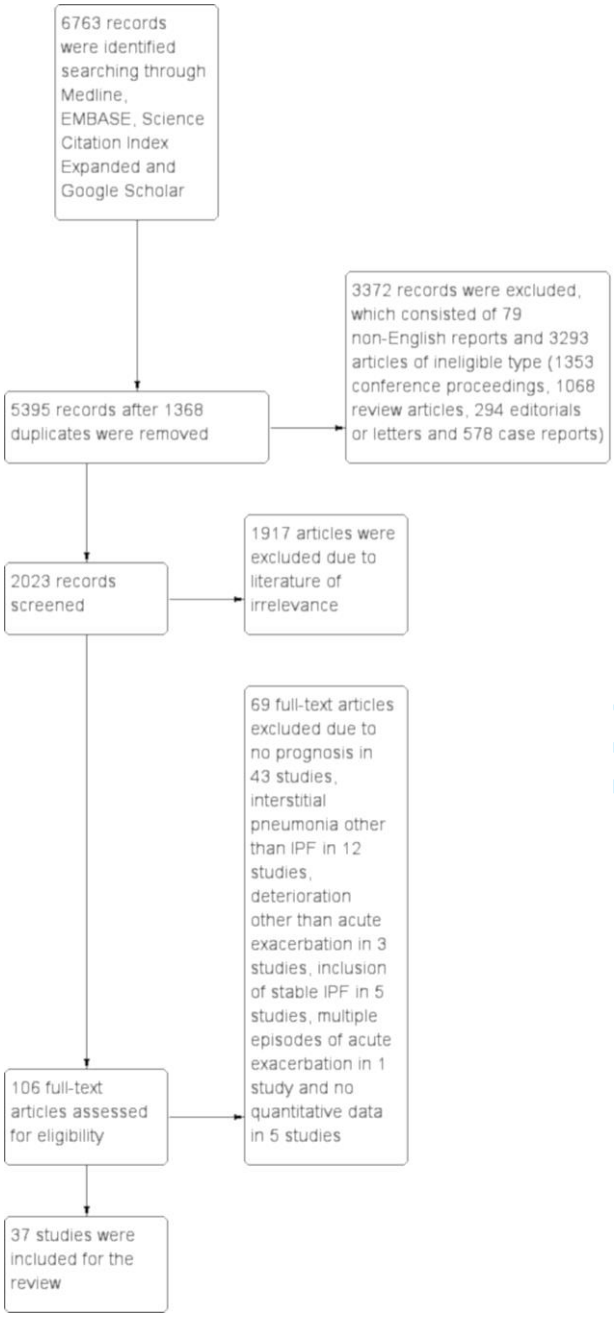
a, A total of 5 clinical information was determined as prognostic factors from 30 potential prognostic factors based on the consistent and significant result on both univariate and multivariate analyses.

b, ‘uni’ indicating univariate analysis while ‘multi’ indicating multivariate analysis.

c, N/A indicating not applicable due to only one study available.

AE, acute exacerbation; APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; HRCT, high resolution computed tomography; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio, WBC, white blood cell;

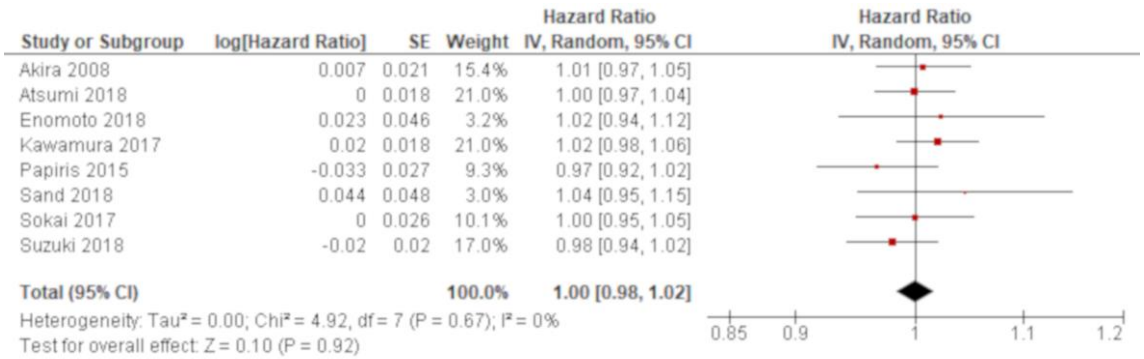
Supplementary e-Figure



Supplementary e-Figure 1. Study flow diagram

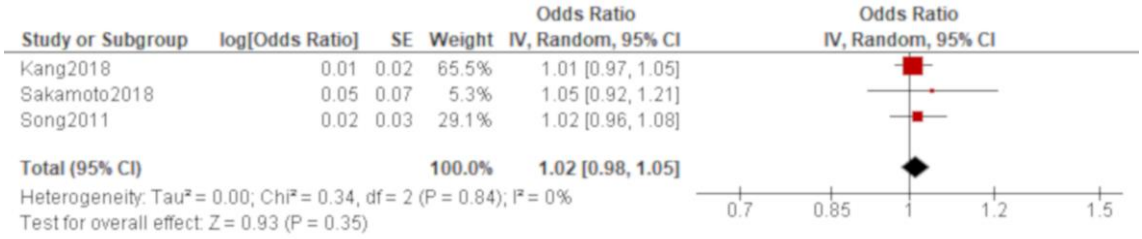
A total of 6763 reports were identified through Medline, EMBASE, Science Citation Index Expanded and Google Scholar. After excluding 1368 duplicates, 79 non-English records, 3293 reports of ineligible types (consisting of 1353 conference proceedings,

1068 review articles, 294 editorials or letters and 578 case reports) and 1917 irrelevant articles, the remaining 106 reports were obtained as full-texts. Out of these, 69 reports were excluded due to no prognosis in 43 studies, interstitial pneumonia other than idiopathic pulmonary fibrosis (IPF) in 12 studies, deterioration other than acute exacerbation in 3 studies, inclusion of stable IPF in 5 studies, multiple episodes of acute exacerbation in 1 study and no quantitative data in 5 studies. Finally, 37 articles/studies were eligible for this review.



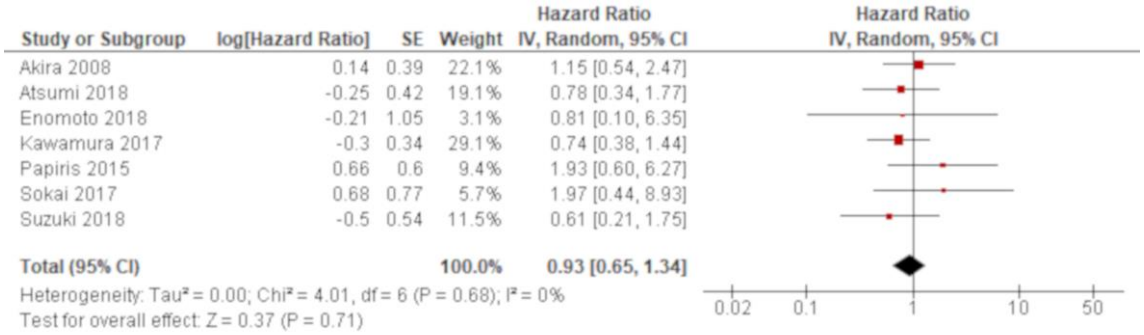
Supplementary e-Figure 2. Forrest plot of the result of univariate analysis for age (combined by hazard ratio)

The result of univariate analysis in 8 studies was pooled for meta-analysis and a total of 405 patients were included. Age was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.00 (95% confidence interval: 0.98 to 1.02, p=0.92). There was no heterogeneity (chi^2=4.92, p=0.67, I^2=0%).



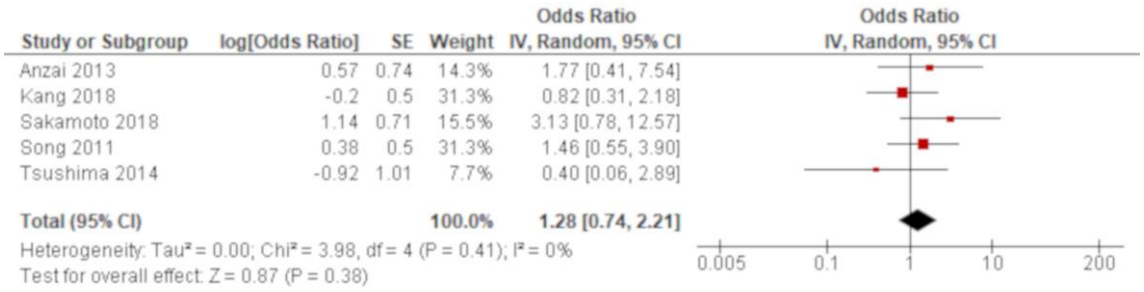
Supplementary e-Figure 3. Forrest plot of the result of univariate analysis for age (combined by odds ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 236 patients were included. Age was not significantly associated with all-cause mortality with an odds ratio (OR) of 1.02 (95% confidence interval: 0.98 to 1.05, p=0.35). There was no heterogeneity (chi^2=0.34, p=0.84, I^2=0%).



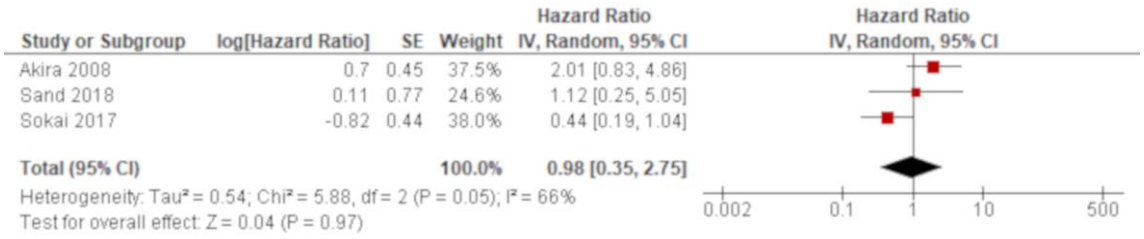
Supplementary e-Figure 4. Forrest plot of the result of univariate analysis for sex (male vs. female) (combined by hazard ratio)

The result of univariate analysis in 7 studies was pooled for meta-analysis and a total of 377 patients were included. Men were not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.93 (95% confidence interval: 0.65 to 1.34, p=0.71). There was no heterogeneity (chi^2=4.01, p=0.68, I^2=0%).



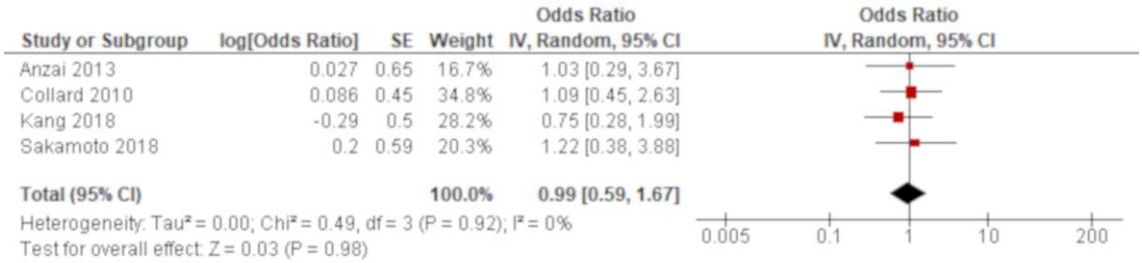
Supplementary e-Figure 5. Forrest plot of the result of univariate analysis for sex (male vs. female) (combined by odds ratio)

The result of univariate analysis in 5 studies was pooled for meta-analysis and a total of 306 patients were included. Men were not significantly associated with all-cause mortality with an odds ratio (OR) of 1.28 (95% confidence interval: 0.74 to 2.21, p=0.38). There was no heterogeneity (chi^2=3.98, p=0.41, I^2=0%).



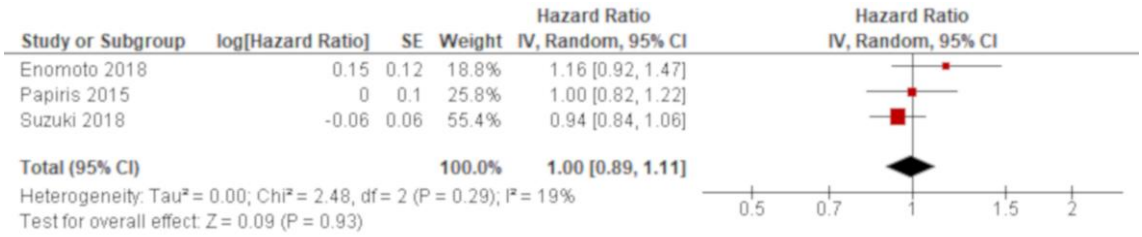
Supplementary e-Figure 6. Forrest plot of the result of univariate analysis for smoking history (ever-smoker vs. never-smoker) (combined by hazard ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 145 patients were included. Smoking history was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.98 (95% confidence interval: 0.35 to 2.75, p=0.97). There was considerable heterogeneity with statistical significance (chi^2=5.88, p=0.05, I^2=66%). The 95% prediction interval ranged from 0.0000 to 95377. All studies were conducted in Japan and implemented nearly the same definition of AE of IPF. One study (Sokai 2017 [62]) demonstrated the effect estimate in the opposite direction from the other two studies. It included over 50 patients and analysed 180-day all-cause mortality whereas the other two studies included over 50 or fewer than 50 patients and analysed in-hospital or overall all-cause mortality.



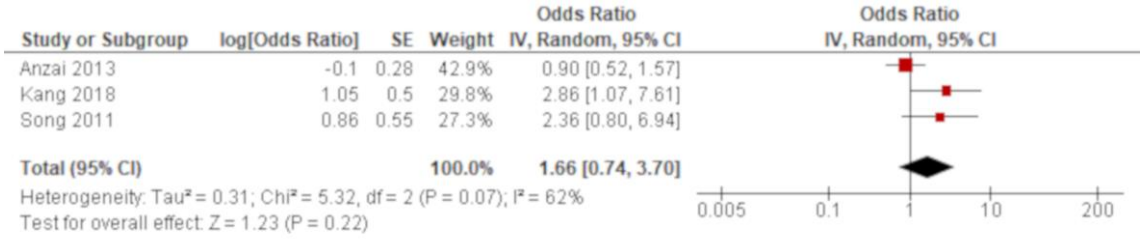
Supplementary e-Figure 7. Forrest plot of the result of univariate analysis for smoking history (ever-smoker vs. never-smoker) (combined by odds ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. Smoking history was not significantly associated with all-cause mortality with an odds ratio (OR) of 0.99 (95% confidence interval: 0.59 to 1.67, p=0.98). There was no heterogeneity (chi^2=0.49, p=0.92, I^2=0%).



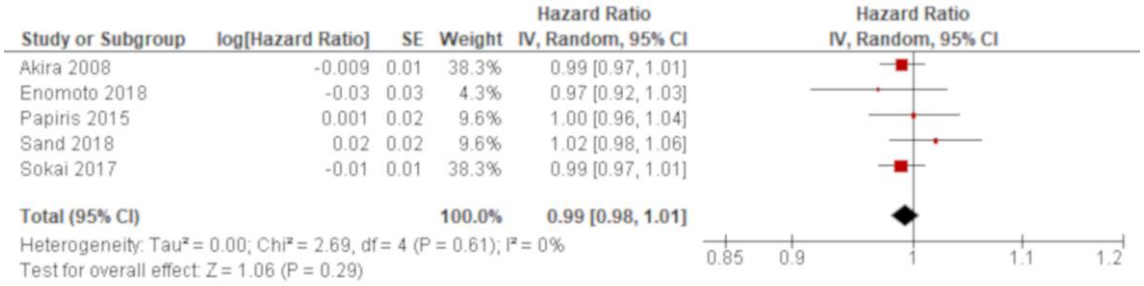
Supplementary e-Figure 8. Forrest plot of the result of univariate analysis for smoking history (pack-year)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 116 patients were included. Smoking history was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.00 (95% confidence interval: 0.89 to 1.11, p=0.93). There was mild heterogeneity with no statistical significance (chi^2=2.48, p=0.29, I^2=19%). The 95% prediction interval ranged from 0.51 to 1.97.



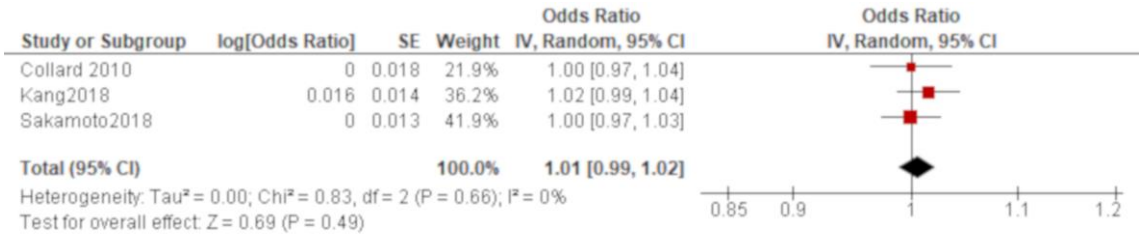
Supplementary e-Figure 9. Forrest plot of the result of univariate analysis for fever

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 206 patients were included. Fever was not significantly associated with all-cause mortality with an odds ratio (OR) of 1.66 (95% confidence interval: 0.74 to 3.70, p=0.22). There was considerable heterogeneity with statistical significance (chi^2=5.32, p=0.07, I^2=62%). The 95% prediction interval ranged from 0.0003 to 10770. All studies implemented the same definition of AE of IPF. One study (Anzai 2013 [37]), which was conducted in Japan, demonstrated the effect estimate in the opposite direction from the other two studies. It included 50 patients and analysed overall all-cause mortality. The other two studies, which were conducted in Korea, included over 50 patients and analysed in-hospital all-cause mortality.



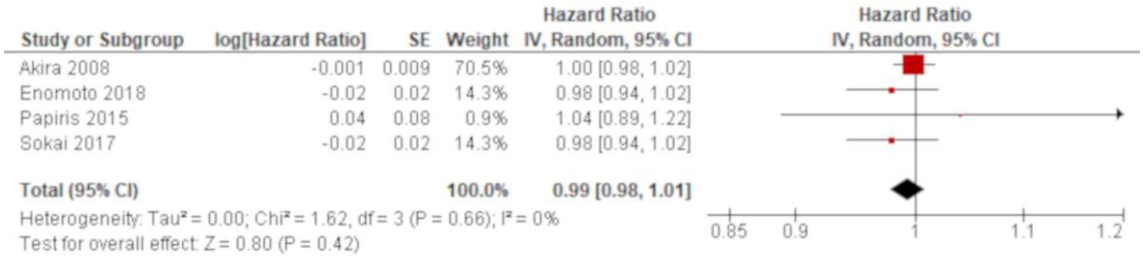
Supplementary e-Figure 10. Forrest plot of the result of univariate analysis for percentage of predicted value of forced vital capacity (%FVC) (combined by hazard ratio)

The result of univariate analysis in 5 studies was pooled for meta-analysis and a total of 199 patients were included. %FVC was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.98 to 1.01, p=0.29). There was no heterogeneity (chi^2=2.69, p=0.61, I^2=0%).



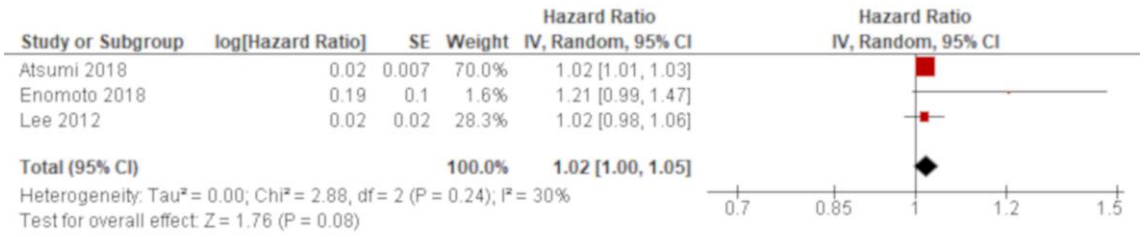
Supplementary e-Figure 11. Forrest plot of the result of univariate analysis for percentage of predicted value of forced vital capacity (%FVC) (combined by odds ratio)

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 193 patients were included. %FVC was not significantly associated with all-cause mortality with an odds ratio (OR) of 1.01 (95% confidence interval: 0.99 to 1.02, p=0.49). There was no heterogeneity (chi^2=0.83, p=0.66, I^2=0%).



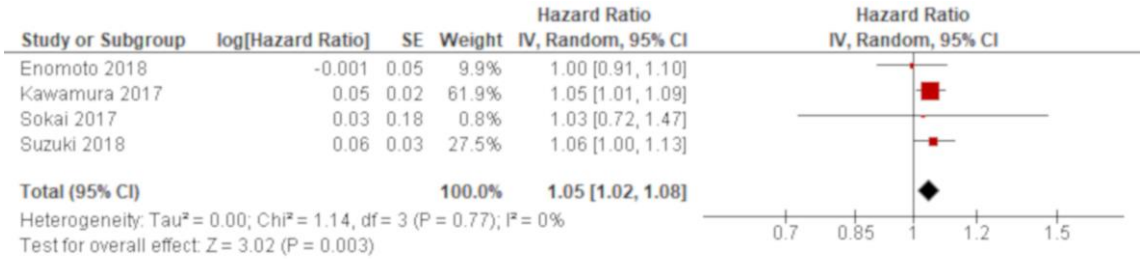
Supplementary e-Figure 12. Forrest plot of the result of univariate analysis for percentage of predictive value of diffusion capacity of the lung for carbon monoxide (%DLCO)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 171 patients were included. %DLCO was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.98 to 1.01, p=0.42). There was no heterogeneity (chi^2=1.62, p=0.66, I^2=0%).



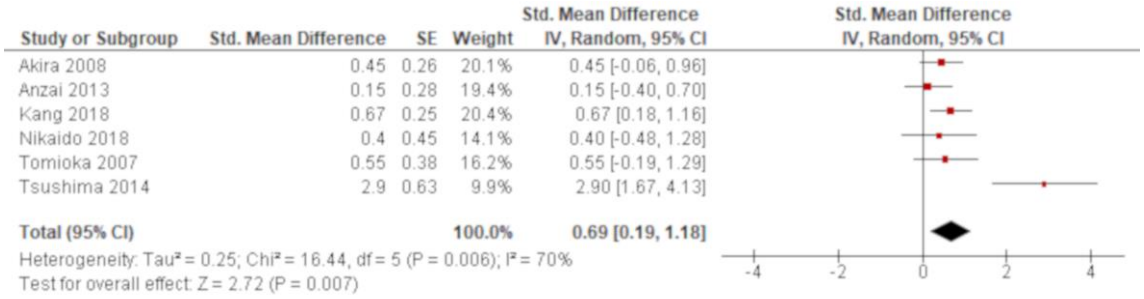
Supplementary e-Figure 13. Forrest plot of the result of univariate analysis for extent of abnormality on high resolution computed tomography (HRCT) scan

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 120 patients were included. Extent of abnormality on HRCT scan was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.00 to 1.05, p=0.08). There was moderate heterogeneity with no statistical significance (chi^2=2.88, p=0.24, I^2=30%). The 95% prediction interval ranged from 0.85 to 1.23.



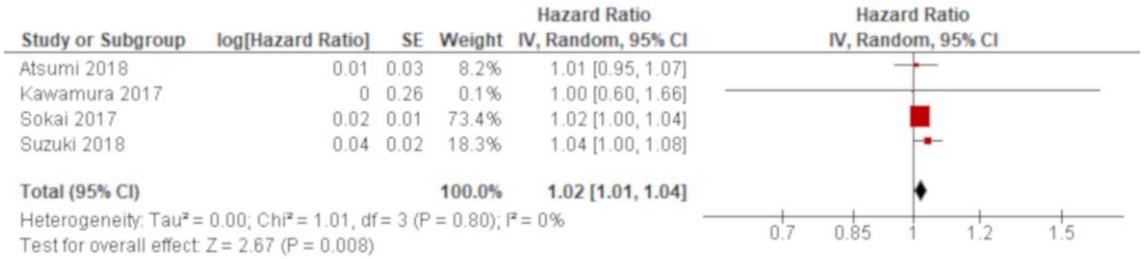
Supplementary e-Figure 14. Forrest plot of the result of univariate analysis for C-reactive protein (CRP) (combined by hazard ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. CRP was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.05 (95% confidence interval: 1.02 to 1.08, p=0.003). There was no heterogeneity (chi^2=1.14, p=0.77, I^2=0%).



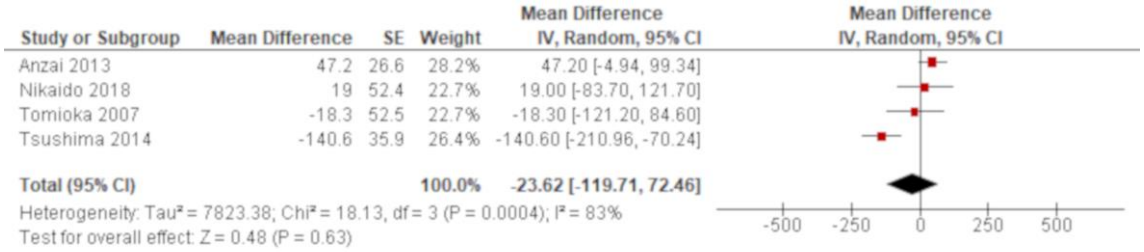
Supplementary e-Figure 15. Forrest plot of the result of univariate analysis for C-reactive protein (CRP) (combined by standardized mean difference)

The result of univariate analysis in 6 studies was pooled for meta-analysis and a total of 242 patients were included. CRP was significantly associated with all-cause mortality with a standardized mean difference (SMD) of 0.69 (95% confidence interval: 0.19 to 1.18, p=0.007). There was substantial heterogeneity (chi^2=16.44, p=0.006, I^2=70%). The 95% prediction interval ranged from -0.86 to 2.24. All studies except for one study (Kang 2018 [47]) were conducted in Japan and most of these studies included 50 or fewer patients. All studies implemented nearly the same definition of AE of IPF. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other five studies. It analysed 28-day all-cause mortality whereas the other five studies analysed either in-hospital, 60-day, 3-month or overall all-cause mortality. Meta-analysis excluding this study demonstrated a SMD of 0.45 (95%CI: 0.19 to 0.72) with no heterogeneity (chi^2=2.00, p=0.74, I^2=0%).



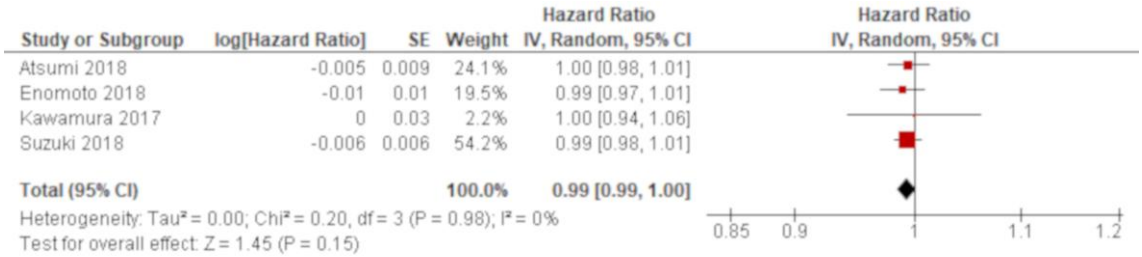
Supplementary e-Figure 16. Forrest plot of the result of univariate analysis for Krebs von den Lungen-6 (KL-6) (combined by hazard ratio)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 265 patients were included. KL-6 was significantly associated with all-cause mortality with a hazard ratio (HR) of 1.02 (95% confidence interval: 1.01 to 1.04, p=0.008). There was no heterogeneity (chi^2=1.01, p=0.80, I^2=0%).



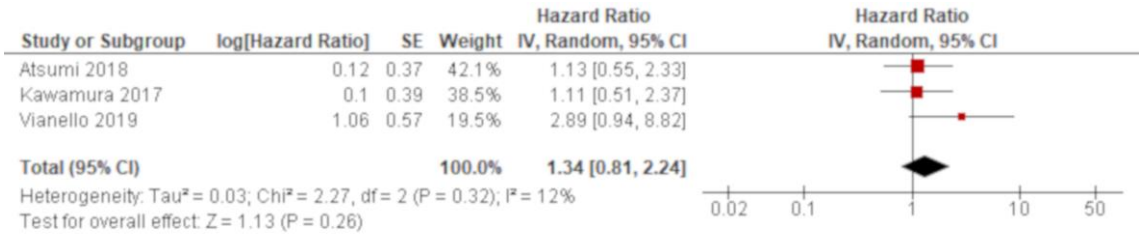
Supplementary e-Figure 17. Forrest plot of the result of univariate analysis for Krebs von den Lungen-6 (KL-6) (combined by mean difference)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 118 patients were included. KL-6 was not significantly associated with all-cause mortality with a mean difference (MD) of -23.6 (95% confidence interval: -119.7 to 72.5, p=0.63). There was substantial heterogeneity with statistical significance (chi^2=18.13, p=0.0004, I^2=83%). The 95% prediction interval ranged from -458.7 to 411.5. All studies were conducted in Japan and included 50 or fewer patients. All studies implemented nearly the same definition of AE of IPF. The effect of one study (Tsushima 2014 [67]) was extremely different from that of the other three studies. It analysed 28-day all-cause mortality whereas the other three studies analysed either in-hospital, 60-day or overall all-cause mortality. Meta-analysis excluding this study demonstrated an MD of 31.3 (95%CI: -11.1 to 73.7) with no heterogeneity (chi^2=1.30, p=0.52, I^2=0%).



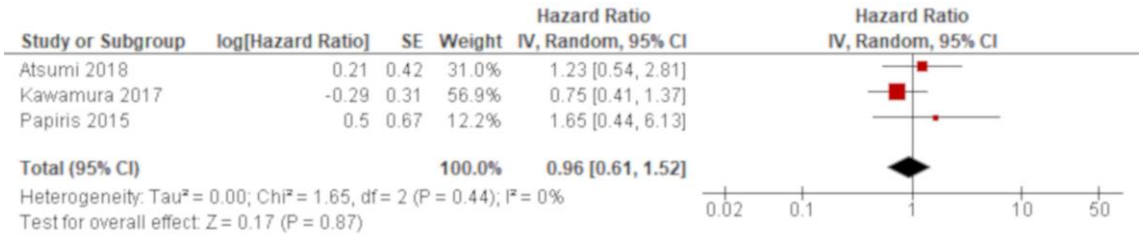
Supplementary e-Figure 18. Forrest plot of the result of univariate analysis for surfactant protein-D (SP-D)

The result of univariate analysis in 4 studies was pooled for meta-analysis and a total of 243 patients were included. SP-D was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.99 (95% confidence interval: 0.99 to 1.00, p=0.15). There was no heterogeneity (chi^2=0.20, p=0.98, I^2=0%).



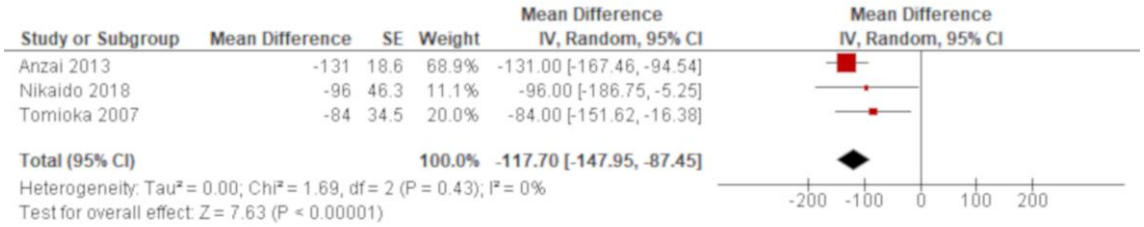
Supplementary e-Figure 19. Forrest plot of the result of univariate analysis for pirfenidone therapy before acute exacerbation

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 164 patients were included. Pirfenidone therapy before acute exacerbation was not significantly associated with all-cause mortality with a hazard ratio (HR) of 1.34 (95% confidence interval: 0.81 to 2.24, p=0.26). There was mild heterogeneity with no statistical significance (chi^2=2.27, p=0.32, I^2=12%). The 95% prediction interval ranged from 0.02 to 75.6.



Supplementary e-Figure 20. Forrest plot of the result of univariate analysis for corticosteroid therapy before acute exacerbation

The result of univariate analysis in 3 studies was pooled for meta-analysis and a total of 161 patients were included. Corticosteroid therapy before acute exacerbation was not significantly associated with all-cause mortality with a hazard ratio (HR) of 0.96 (95% confidence interval: 0.61 to 1.52, p=0.87). There was no heterogeneity (chi^2=1.65, p=0.44, I^2=0%).



Supplementary e-Figure 21. Forrest plot of the result of univariate analysis for partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio (combined by mean difference)

As there was substantial heterogeneity in the result of meta-analysis using MD for PaO2/FiO2 ratio (Figure 4), meta-analysis was re-conducted after excluding one study (Tsushima 2014 [67]) that demonstrated an extremely different effect estimate from the other studies. The result was significant with an MD of -117.7 (95%CI: -148.0 to -87.5) and no heterogeneity was identified (chi^2=1.69, p=0.43, I^2=0%).

Supplementary e-Appendix: Search terms for each electronic database

Medline (Ovid)

1 exp Pulmonary Fibrosis/

2 exp Idiopathic Pulmonary Fibrosis/

3 exp Lung Diseases, Interstitial/

4 (pulmonary adj3 fibros$).mp.

5 (interstitial adj3 pneumoni$).mp.

6 exp Disease Progression /

7 (acute adj3 exacerbation?).mp.

8 (disease adj3 progression?).mp.

9 (disease adj3 exacerbation?).mp.

10 (deterioration?).mp.

11 incidence.sh.

12 exp Mortality/

13 follow-up studies.sh.

14 prognos$.tw.

15 predict$.tw.

16 course$.tw.

17 (1 or 2 or 3 or 4 or 5)

18 (6 or 7 or 8 or 9 or 10)

19 (11 or 12 or 13 or 14 or 15 or 16)

20 (17 and 18 and 19)

21limit 20 to yr="2002 -Current"

EMBASE (Ovid)

1 exp fibrosing alveolitis/

2 exp interstitial pneumonia/

3 exp lung fibrosis /

4 (pulmonary adj3 fibros$).mp.

5 (interstitial adj3 pneumoni$).mp.

6 exp disease exacerbation /

7 exp deterioration /

8 (acute adj3 exacerbation?).mp.

9 (disease adj3 progression?).mp.

10 (disease adj3 exacerbation?).mp.

11 risk$.mp.

12 diagnos$.mp.

13 follow-up.mp.

14 ep.fs.

15 outcome.tw.

16 exp disease course/

17 (1 or 2 or 3 or 4 or 5)

18 (6 or 7 or 8 or 9 or 10)

19 (11 or 12 or 13 or 14 or 15 or 16)

20 (17 and 18 and 19)

21 limit 20 to yr="2002 -Current"

Science Citation Index Expanded (Web of Science)

#1 TS=("interstitial NEAR/3 lung NEAR/3 disease$") OR TS=("interstitial NEAR/3 pneumonia$") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*")

#2 TS=(acute NEAR/3 exacerbation$) OR TS=(disease NEAR/3 progression$) OR TS=(disease NEAR/3 exacerbation$) OR TS=(deterioration$)

#3 TS=(prognos*) OR TS=(mortality) OR TS=(outcome) OR TS=(course$) OR TS=(follow-up) OR TS=(predict*) OR TS=(incidence) OR TS=(risk)

#4 #1 AND #2 AND #3

#5 #4 AND (2002-2019)

Google scholar

("acute exacerbation" OR "disease progression" OR "disease exacerbation") ("interstitial lung disease" OR "usual interstitial pneumonia" OR "idiopathic pulmonary fibrosis") (prognosis OR mortality OR outcome)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 e-Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 8 e-Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-9 e-Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9 e-Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 10-12 e-Table 4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 10-12 e-Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Checklist items for Meta-analyses of Observational Studies in Epidemiology (MOOSE)	Reported on Page
Reporting of background should include	
• Problem definition	Page 4-5
• Hypothesis statement	Not described
• Description of study outcome(s)	Page 5
• Type of exposure or intervention used	Page 5
• Type of study designs used	Page 5
• Study population	Page 5
Reporting of search strategy should include	
• Qualifications of searchers (eg, librarians and investigators)	Page 6
• Search strategy, including time period included in the synthesis and keywords	Page 6 e-Appendix
• Effort to include all available studies, including contact with authors	Page 6
• Databases and registries searched	Page 6
• Search software used, name and version, including special features used (eg, explosion)	Not described
• Use of hand searching (eg, reference lists of obtained articles)	Page 6
• List of citations located and those excluded, including justification	e-Figure 1
• Method of addressing articles published in languages other than English	Page 5
• Method of handling abstracts and unpublished studies	Page 6
• Description of any contact with authors	Page 6
Reporting of methods should include	
• Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Not described

• Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Not described
• Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Not described
• Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Not described
• Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 6
• Assessment of heterogeneity	Page 7
• Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 7
• Provision of appropriate tables and graphics	e-Figure 1 (study flow diagram)
Reporting of results should include	
• Graphic summarizing individual study estimates and overall estimate	e-Table 4, 5
• Table giving descriptive information for each study included	e-Table 1
• Results of sensitivity testing (eg, subgroup analysis)	Page 12
• Indication of statistical uncertainty of findings	Page 10-12 e-Table 4, 5
Reporting of discussion should include	
• Quantitative assessment of bias (eg, publication bias)	Not described
• Justification of exclusion (eg, exclusion of non-English-language citations)	Not described
• Assessment of quality of included studies	Page 16
Reporting of conclusions should include	
• Consideration of alternative explanations for observed results	Page 15
• Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 16

• Guidelines for future research	Page 16
• Disclosure of funding source	Page 17

From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.