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Outcomes of patients with acute exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids: a systematic review and meta-analysis

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Abstract

Background Acute exacerbation of idiopathic pulmonary fibrosis (IPF) is the most severe complication and one of the main causes of death in these patients. No proven effective therapies have been reported until now but high-dose corticosteroids are suggested by the international guidelines.

Methods A search of the scientific evidence was carried out using PubMed, Embase, and Scopus.
Observational and experimental studies describing clinical outcomes in adult patients with acute exacerbations of IPF treated with corticosteroids were included.

Results 32 studies were selected for the qualitative and quantitative analysis. In patients treated only with corticosteroids, the pooled 90-day and in-hospital mortality rate was 42% (95% CI = 19-67%) and 43% (95% CI = 30-56%), respectively.
Pooled 90-day mortality in patients treated with methylprednisolone at doses of 1000 mg/day was higher than in those treated with 500-1000 mg/day (i.e. 10 mg/kg/day) (54% (95% CI = 11-94%) VS. 39% (95% CI = 12 to 71%)). In patients with background antifibrotic therapy, the pooled 90-days mortality was of 39% (95% CI = 25-54%) while in those without was of 49% (95% CI = 10-89%).
The 90-day and in -hospital mortality for patients receiving concomitant immunosuppressive therapy was 37% (95% CI = 29-46%) and 35% (95% CI = 12-62%), respectively. The overall 1-year mortality was 43% (95%CI = 30-56%).

Conclusions Patients with acute exacerbation of IPF treated with corticosteroids show a high short- and long-term mortality. Those treated with lower steroid doses and with background antifibrotic therapy show the highest short-term survival rates.

Keywords IPF, Acute exacerbation, Idiopathic pulmonary fibrosis, Corticosteroids, Mortality, Antifibrotic therapy

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Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing, and progressive interstitial lung disease (ILD) of unknown etiology [1, 2]. Acute exacerbation of IPF (AE-IPF), which is the most severe complication and one of the main causes of death [2–5], is defined as a worsening of dyspnea and/or gas exchange within 1 month, associated with new bilateral ground-glass opacities/consolidation on a background of fibrotic interstitial lung disease, not successfully explained by cardiac failure or fluid overload [3, 4].

It can occur at any point of the natural history of IPF and can occasionally be its presenting manifestation [3, 4], showing a high in-hospital mortality and a median survival, after the first episode, of 3–4 months [2–4].

AE-IPF may be idiopathic or prompted by other conditions (e.g., infections, drugs, surgery) but etiology remains uncertain in many cases [4].

Results from clinical trials and observational studies suggest that background antifibrotic therapy might reduce the risk of acute exacerbation [6, 7]. No proven effective therapies for AE-IPF have been described [2–6], with the only exception of a weak recommendation for corticosteroids [8], without clear dosing and duration [2, 8]. High-dose steroids (methylprednisolone 500–1000 mg per day for 3 days or equivalent, followed or not by a slow tapering) are usually administered worldwide [9]. However, a recent retrospective study showed no evidence that corticosteroid use improves outcomes in AE-IPF patients admitted to the hospital and that it may contribute to reduced overall survival following an exacerbation, when compared with patients not receiving this treatment [10].

Adjunctive therapy with immunosuppressants has been described [11–13]. However, a recent randomized controlled trial found that cyclophosphamide did not improve prognostic outcomes when combined with corticosteroids [13].

This systematic review and meta-analysis aimed to provide an update on prognostic outcomes of patients with AE-IPF treated with corticosteroids. Outcomes related to the presence of background antifibrotic therapy, use of other immunosuppressive therapy, and different doses of corticosteroids were also assessed.

Methods

Study design and search strategy

A systematic review was conducted to identify observational and experimental studies addressing the outcomes of patients with AE-IPF treated with corticosteroids.

Three electronic databases (i.e., PubMed, Embase, and Scopus) were used to detect articles published until March 2025.

To retrieve the scientific evidence from the abovementioned databases, strings were created using the following single and combined key-words: corticosteroid, glucocorticoids, idiopathic pulmonary fibrosis, IPF, interstitial lung disease, acute exacerbation, exacerbation, treatment, therapy, respiratory failure, mortality.

The study protocol was registered at PROSPERO international database (CRD42023388678), and the process of systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [14].

Selection criteria

Observational and experimental studies focusing on epidemiological aspects and clinical outcomes in adult populations treated for AE-IPF were included.

Articles were excluded for one of the following criteria: (1) unclear primary and secondary outcomes; (2) studies performed in animals; (3) case-reports or case series which enrolled less than 5 patients; (4) editorials, correspondences, reviews, book chapters, guidelines, conference proceedings and congresses; abstracts; surveys; (5) languages other than English; (6) studies on interstitial lung diseases other than IPF.

Authors carefully and independently evaluated titles and abstracts of the records for the selection of the full texts, which were assessed for their eligibility by two authors independently (CA and JC). Discrepancies during the selection of the articles and extraction of the variables were solved by the intervention of a third senior author (MM).

Data extraction

Qualitative and quantitative variables were collected in an ad hoc electronic form. The following variables were collected: first author of the article; title of the article; year when the study was published; year/s when the study was conducted; epidemiological study design; country where the study was carried out; sample size; gender; age; ethnicity; smoking status; respiratory and cardiovascular comorbidities; criteria for IPF and AE-IPF diagnosis; functional characteristics and ongoing treatments of patients enrolled in the studies; presence of identifiable AE-IPF triggers; respiratory failure; treatment of respiratory failure; use of corticosteroids (dosage, duration, type); use of other concomitant treatments during exacerbations (i.e. immunosuppressants, antibiotics), presence/absence of background antifibrotics therapy; cause of death; mean survival; in-hospital mortality; 90-days mortality; 1-year mortality; rate of hospital re-admission. Data independently extracted by the authors were cross-checked for the detection of inconsistencies.

Study quality assessment

The inter-rater agreement for study selection and data extraction was nearly 100%, with only minimal inconsistencies addressed and solved through consensus and, when necessary, the involvement of a third party for final opinion (GS). To guide the systematic review process, the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) were followed [14].

The methodological quality and bias of the studies were assessed using specific tools for systematic review, tailored to the study design.

The Joanna Briggs Institute Critical Appraisal tools (JBI), applied for analytical cross-sectional studies was used for all studies where the control group was missing [15]. A total of eight items per study were considered and the risk of bias was categorized by the number of positive "Yes" answers in high-risk (i.e., below 50%), moderate-risk (i.e., 50%-75%), and low-risk (i.e., above 75%).

The Newcastle Ottawa (NOS) scale was used to assess the quality of cohort studies, evaluating the selection of participants, comparability, and outcome through, respectively, four, two, and three items, and categorization into good, fair, and poor quality [16].

In the RCT studies, the risk of bias was evaluated by the JBI scale, through nine items and calculating the number of affirmative answers [15]. The risk of bias was classified as high, moderate, or low if the percentage of positive answers was, respectively, ≤ 49%, between 50% and 75%, or above 75%.

Statistical analysis

Descriptive statistics were used to summarize the main findings and demographic characteristics of the included studies. Meta-analytic estimates were calculated and reported alongside with measures of heterogeneity. Forest plots were generated to illustrate the variability across studies, displaying 95% confidence intervals (CIs) for the proportions of study-pooled outcomes.

Heterogeneity among studies was assessed using the I^2 statistic, with values exceeding 50% considered indicative of substantial heterogeneity. Accordingly, both fixed- and random-effects models were applied to account for potential between-study variability. Publication bias was evaluated visually using funnel plots and statistically assessed with Egger's test. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using STATA 17 (StataCorp, College Station, TX, USA), StatsDirect version 3.1.12 (StatsDirect Ltd., London, UK), and Meta-DiSc 2.0 software.

Results

Study selection

The search of the electronic databases found 6784 records and 3792 potential studies were identified for screening after duplicate removal.

Subsequently, a total of 88 studies were screened by titles and abstracts; seven of those were excluded (not retrieved).

A total of 81 full texts were evaluated and 48 were excluded for the following reasons: no data on mortality ($n = 34$), other topics ($n = 11$), letter ($n = 1$), survey ($n = 1$), abstract ($n = 1$) (Fig. 1). Finally, 33 studies were selected for the qualitative and quantitative analysis.

Characteristics of the selected studies

The articles describe studies conducted between 1988 and 2022 [17, 18] and published between 2003 and 2023 [17–20] (Table 1).

The following countries were involved in the selected studies: Japan (n = 22, 66.6%) [11, 17–37], South Korea (n = 3, 9.1%) [20, 38, 39], Canada (n = 2, 6.1%) [40, 41], China (n = 2, 6.1%) [42, 43], France (n = 2, 6.1%) [13, 44], Italy (n = 1, 3.0%) [12], Spain (n = 1, 3.0%) [45], USA (n = 1, 3.0%) [10].

The study designs were mainly observational, with 28 out of 32 (84.8%) studies being retrospective [10–12, 17, 18, 20–22, 24, 26–36, 38–45] and 2 (6.1%) being prospective [23, 25]. Three (9.1%) studies were randomized controlled trials [13, 37, 42]. Most studies (21/33, 63.6%) were single center [10–12, 20–27, 29, 30, 33, 38–45], whereas twelve (36.4%) were multi-center [13], 40– [18, 28, 31, 32, 34–36]. The sample sizes of the selected studies ranged from 9 to 5,616 patients [18, 45] (Table 1).

Characteristics of the study samples

Main clinical characteristics

The mean age of recruited patients ranged from 64 to 78 years [36, 38], and the majority were males (Table 1). Most patients had a history of smoking, with percentages as high as 93% in some studies [27]. Additionally, a subset of patients had co-existing emphysema (up to 48.6%) and chronic respiratory failure (up to 47.6%) [10, 44]. Fewer data were available on lung cancer and chronic cardiovascular disease (Table 1 supplement) [18, 20, 27, 31, 34, 35, 38, 42, 45]. Many patients received background antifibrotic and/or immunosuppressive therapies [13, 19, 20, 22, 25–27, 29, 30, 32, 33, 35–43, 45]. Antifibrotic therapy (pirfenidone or nintedanib) was recorded in several studies, with percentages ranging from 0% to 56% [21,

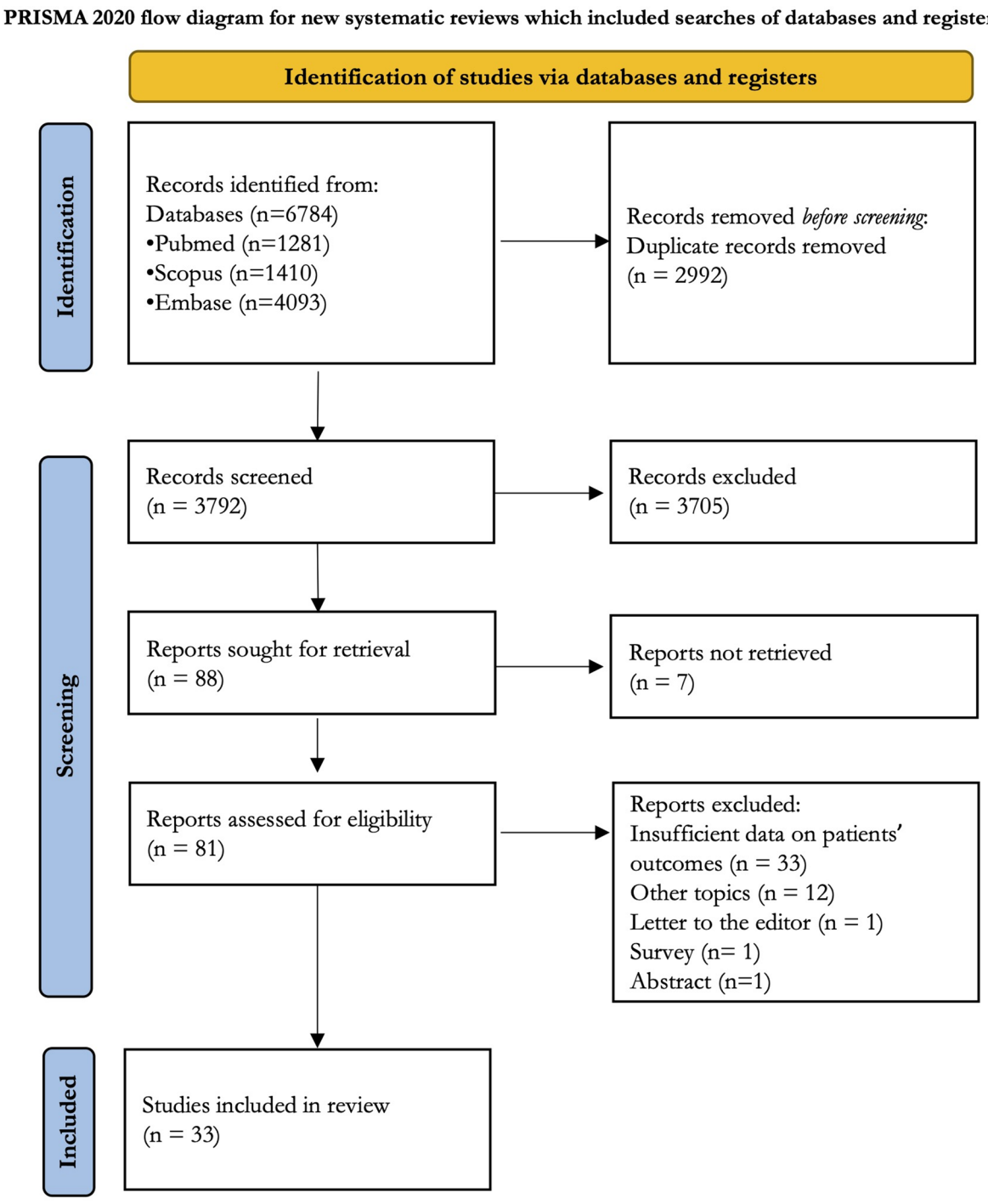

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram

29]. Immunosuppressive therapies were also frequently used (up to 88.8% of the patients) [45]. N-acetylcysteine (NAC) therapy was described in four studies (Table 1 supplement) [24,32,35,43].

Clinical characteristics and treatment of acute exacerbations

The diagnosis of IPF and AE-IPF was performed following four [1, 8, 46, 47] and three different statements/guidelines [3, 4, 46], respectively, depending on the study

Table 1 Summary of the included studies

Author, year	Country	Study period	Study design	Mono/ Multicentre	Sample size	Male, *n* (%)	Age, mean ± (SD) or median (IQR or range)	AE-IPF, *n*	AE-IPF, %	Criteria for IPF diagnosis	Criteria for AE diagnosis
Inase, 2003 [19]	Japan	1990–1999	Retrospective	Multicentric	13	10 (3.0)	67 (8.7)	13	100	2000	2000
Al-Hameed, 2004 [17]	Canada	1988–2000	Retrospective	Multicentric	25	23 (92.0)	69 (11)	25	100	2000	2000
Sakamoto, 2010 [11]	Japan	1994–2004	Retrospective	Monocentric	233	21 (95.4)	70.5 (11.5)	47	20.7	-	2007
Song, 2011[39]	South Korea	1990–2009	Retrospective	Monocentric	96	69 (71.9)	64.3 (8.9)	96	100	2002	2007
Horita, 2011 [23]	Japan	2001–2010	Retrospective	Monocentric	15	6 (40.0)	74.8	15	100	-	2007
Simon-Blancal, 2012 [44]	France	2002–2009	Retrospective	Monocentric	27	22 (81.5)	69.0 (31–81) (range)	27	100	2002	2007
Isshiki, 2015 [24]	Japan	2006–2013	Retrospective	Monocentric	41	36 (87.8)	73 (6)	41	100	2011	2007
Abe, 2015 [25]	Japan	2012–2014	Prospective	Monocentric	22	19 (86.3)	71 (9.3)	16	72.7	2011	2007
Novelli, 2016 [12]	Italy	2009–2013	Retrospective	Monocentric	11	7 (63.6)	65 (55–75) IQR	11	100	2011	2007
Oishi, 2016 [26]	Japan	2006–2014	Retrospective	Monocentric	50	46 (92.0)	71.8 (59–85) range	50	100	2011	2007
Hayakawa, 2016 [27]	Japan	2012–2014	Prospective	Monocentric	37	19 (82.6)	71.2	23	62.1	2011	2007
Atsumi, 2018 [28]	Japan	2008–2017	Retrospective	Monocentric	59	49 (83.0)	74 (66–78) IQR	59	100	2002	2007
Yamazoe, 2018 [29]	Japan	2008–2017	Retrospective	Monocentric	64	54 (84.4)	76.3 (6.9)	64	100	2011	2016
Cuerpo, 2019 [45]	Spain	2003–2014	Retrospective	Monocentric	9	5 (55.6)	77 (10)	9	100	-	2007
Murohashi, 2019 [30]	Japan	2014–2017	Retrospective	Multicentric	17	14 (82.0)	75 (72-79.5) IQR	17	100	-	2016
Okuda, 2019 [31]	Japan	2006–2015	Retrospective	Monocentric	107	82 (76.6)	66.9 (7.1)	39	36	2011	2016
Sakamoto, 2019 [32]	Japan	2008–2017	Retrospective	Monocentric	88	74 (84.0)	74.7 (56–89) range	88	100	2018	2007
Aso, 2019 [33]	Japan	2010–2014	Retrospective	Multicentric	1847	1254 (67.9)	-	1847	100	-	2007
Hozumi, 2019 [34]	Japan	2004–2017	Retrospective	Multicentric	102	87 (85.3)	71.7 (8.2)	102	100	2011	2016
Farrand, 2020 [10]	USA	2010–2018	Retrospective	Monocentric	82	38 (46.0)	66.8 (10)	82	100	2018	2016
Ikuyama, 2020 [35]	Japan	2003–2017	Retrospective	Monocentric	62	53 (85.5)	72 (67–75) IQR	62	100	2018	2007/2016
Arai, 2020 [36]	Japan	2014–2016	Retrospective	Multicentric	85	65 (76.4)	74	85	100	2011	2016
Zhuang, 2020 [43]	China	2014–2018	Retrospective	Monocentric	45	36 (80.0)	66.6	45	100	2011	2016
Kondoh, 2020 [39]	Japan	2016–2018	RCT	Multicentric	82	67 (87.0)	73 (67–78) IQR	82	100	2011	2016
Jang, 2021 [41]	South Korea	2016–2018	Retrospective	Monocentric	182	94 (80.3)	69.4 (9.9)	117	64.2	2018	2016
Adams, 2021 [42]	Canada	2015–2019	Retrospective	Monocentric	89	40 (71.4)	66.8 (8.6)	56	62.9	2018	2016
Horio, 2022 [37]	Japan	2007–2018	Retrospective	Multicentric	62	48 (77.4)	74 (8)	62	100	2018	2007

Table 1 (continued)

Author, year	Country	Study period	Study design	Mono/ Multicentre	Sample size	Male, *n* (%)	Age, mean ± (SD) or median (IQR or range)	AE-IPF, *n*	AE-IPF, %	Criteria for IPF diagnosis	Criteria for AE diagnosis
Naccache, 2022 [13]	France	2016–2018	RCT	Multicentric	119	94 (78.9)	72 (9)	119	100	2011	2007
Anan, 2022 (A) [38]	Japan	2016–2019	Retrospective	Multicentric	822	113 (74.0)	78	153	18.6	2018	2016
Anan, 2022 (B) [38]	Japan	2016–2020	Retrospective	Multicentric	427	160 (70.0)	77	229	53.6	2018	2016
Awano, 2023 [20]	Japan	2010–2018	Retrospective	Multicentric	5616	4167 (74.29)	-	5616	100	-	2016
Li, 2023 [18]	China	2019–2022	RCT	Multicentric	80	51 (63.7)	67.3 (6.2)	80	100	2011	2016
Yamazaki, 2023 [21]	Japan	2008–2019	Retrospective	Monocentric	97	78 (80.4)	75 (6.6)	97	100	2011	2016
Hyung, 2023 [22]	South Korea	2013–2021	Retrospective	Monocentric	238	179 (75.2)	72.3	238	100		2016

SD Standard deviation, *IQR* Interquartile range, *AE-IPF* Acute exacerbation of idiopathic pulmonary fibrosis, *IPF* Idiopathic pulmonary fibrosis, *CPFE* Combined pulmonary fibrosis and emphysema, *RCT* Randomized controlled trial

period (Table 1). Exacerbation triggers were reported in up to 62% of the cases [39]: infections, thoracic surgery or interventional pulmonology procedures, drug toxicity, aspiration, and other surgical interventions [27–30, 38, 41, 44] (Table 2 supplement).

Respiratory failure was a frequent complication on admission [18, 20, 30]; however, this information was not frequently available. Respiratory failure was managed with different respiratory supports: oxygen therapy, high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV).

In particular, IMV was required in 3.2%-84% of the cases, whereas NIMV and HFNC were employed in up to 100% and 27%, respectively (Table 2 supplement) [31, 35, 36, 40].

Deaths during AE-IPF were primarily caused by respiratory failure related to acute exacerbation or to in-hospital complications (e.g., infections and pneumonia) (Table 2 supplement). Median survival after an acute exacerbation was variable, ranging from a few months [22, 25, 39, 41, 44] to more than one year [32, 35, 38, 44] (Table 2 supplement).

Acute exacerbations were treated with high-dose corticosteroids (Table 3 supplement). Methylprednisolone pulses at 1,000 mg/day for 3 days and methylprednisolone at the dosage of 500-1,000 mg/day (i.e., 10 mg/Kg/day) administered for 3 days were the most common prescribed regimens (13, 40.6% and 10, 31.3%, respectively) [10–13], 42– [26, 30–32, 35–38, 41, 43]. In six studies, methylprednisolone was administered at a dosage of 0.5-1 mg/kg/day [10, 20, 35, 38, 43, 45], whereas in the remaining cases, variable regimens were used or no type and/or dosage of the steroid was detailed [27–29, 33, 34, 40].

Type, dose, and duration of corticosteroid tapering varied across studies and involved methylprednisolone, prednisolone, and prednisone for 7 to 180 days [13, 45] (Table 3 supplement).

In addition to corticosteroids, immunosuppressive agents (i.e., cyclosporine A, cyclophosphamide, azathioprine, and tacrolimus) were prescribed in 18–100% of the patients [12, 13, 17, 22–26, 29–38, 44].

The percentage of patients treated with polymyxin-B hemoperfusion (PMX-HP) ranged from 4.7% to 23.5% [32, 34] whereas recombinant thrombomodulin was used in up to 51% [30, 37]. (Table 3 supplement).

Antibiotics were frequently prescribed, with broad-spectrum ones administered in up to 100% of patients [21] (Table 3 supplement).

Outcomes

In patients treated only with corticosteroids, 90-day and in-hospital mortality related to treatment dosage, are displayed in Table 4 supplement and Fig. 2. The majority reported outcomes with a starting dose of 500–1000 mg/day and 1000 mg/day [10–13], 42– [26, 30–32, 35–41]. Hyung et al. reported in-hospital and 90-day mortality of 18.6% and 35.6%, respectively, with a mean starting dose of 500 mg/day, [20].

Two studies reported in-hospital mortality with a starting dose of 1,000 mg/day. The reported mortality rate was 54.6% and 90%, respectively [11, 21] (Table 4 supplement).

Only three studies reported outcomes with a starting dosage of 0.5-1 mg/Kg/day [22, 41, 43]. Song et al. and Hyung et al. reported a in-hospital mortality of 36.3% and

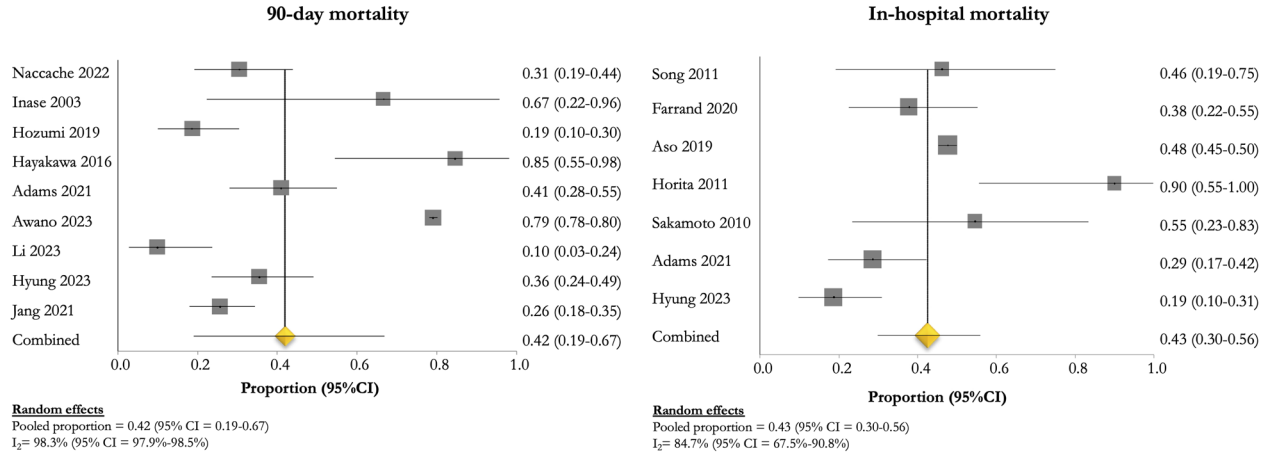

Fig. 2 Pooled 90-day and in-hospital mortality of patients with acute exacerbation of idiopathic pulmonary fibrosis treated only with a corticosteroid therapy regardless of treatment dosage

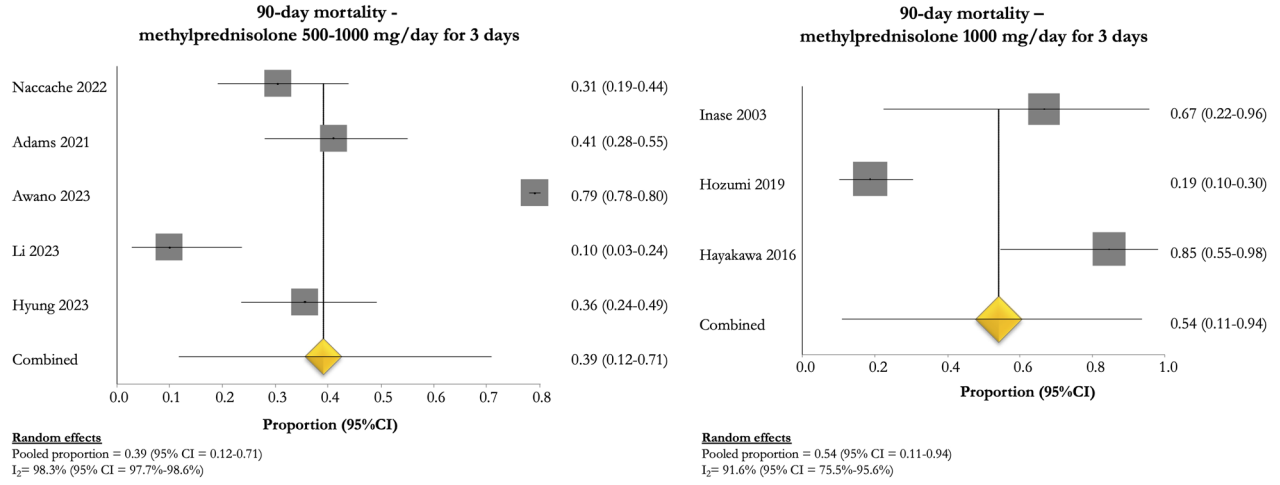

Fig. 3 Pooled 90-day mortality of patients with acute exacerbation of idiopathic pulmonary fibrosis treated only with a corticosteroid therapy related to methylprednisolone starting dosage

50%, respectively, whereas Hyung et al. reported a 90-day mortality of 47.5% [20, 38]. Jang et al. reported a 90-day mortality of 25.6% [39] (Table 4 supplement).

In one study[10], different doses were prescribed but outcomes related to specific dosages were not described. Another study[45] described the mortality rate in the population, but only a group was treated with corticosteroids.

90-day mortality

In patients treated only with corticosteroids, the pooled 90-day mortality rate was 42% (95% CI = 0.19–0.67%) [25, 42] (Fig. 2). Pooled mortality in patients treated with methylprednisolone at doses of 1,000 mg/day was higher than in those treated with 500-1,000 mg/day (i.e., 10 mg/kg/day) (54%; 95% CI = 0.11–0.94% VS. 39%; 95% CI = 0.12 to 0.71%) (Fig. 3).

In patients with background antifibrotic therapy, the pooled 90-day mortality was 39% (95% CI = 0.25–0.54%) whereas in those without was 49% (95% CI = 0.10–0.89%) (Fig. 4).

The pooled 90-day mortality for patients receiving concomitant immunosuppressive therapy was 37% (95% CI = 0.29–0.46%) (Fig. 5).

In-hospital mortality

The pooled in-hospital mortality in patients treated only with steroids was 43% (95% CI = 0.30–0.56%) [20, 21] (Fig. 2). The rate was lower in patients receiving concomitant immunosuppressive therapy 35% (95% CI = 0.12–0.62%) (Fig. 5).

Pooled in-hospital mortality in patients treated with methylprednisolone at doses of 500-1,000 mg/day was 35% (95% CI = 0.19–0.52%) (Fig. 1 supplement).

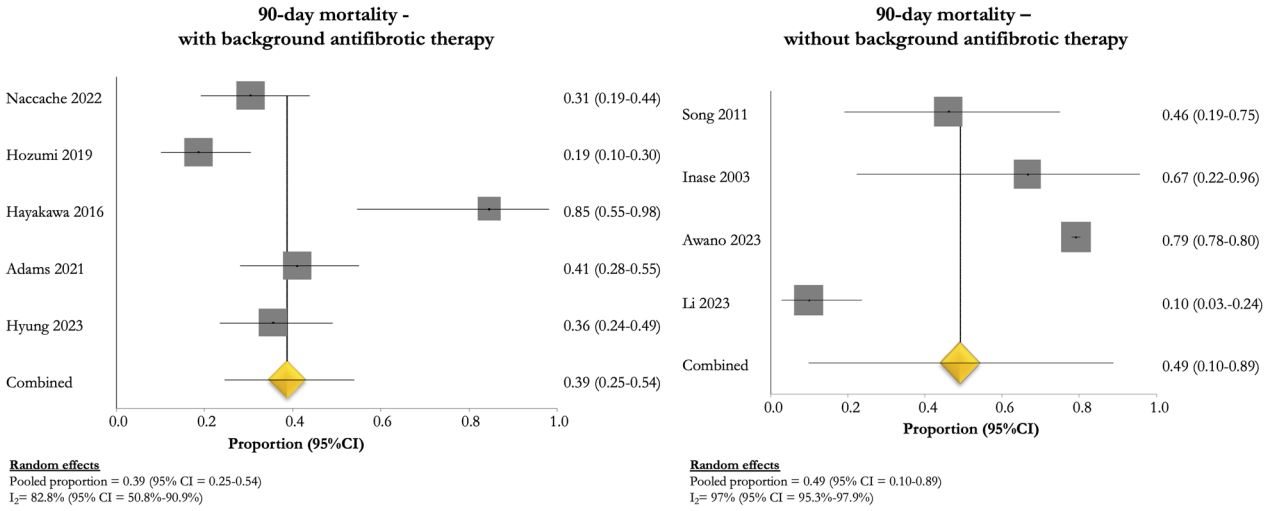

Fig. 4 Pooled 90-day of patients with acute exacerbation of idiopathic pulmonary fibrosis treated with corticosteroid therapy related to background antifibrotic therapy

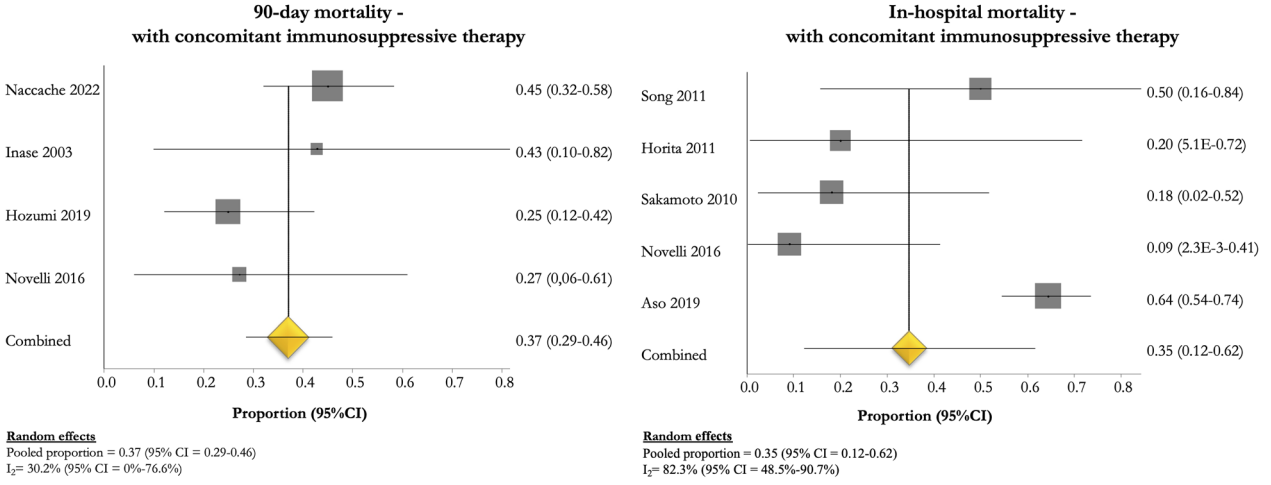

Fig. 5 Pooled 90-days and in-hospital mortality of patients with acute exacerbation of idiopathic pulmonary fibrosis treated with corticosteroid therapy related to concomitant immunosuppressive therapy administration

1-year mortality

The overall 1-year mortality was 43% (95%CI = 0.30–0.56%) [20, 21] (Fig. 2 supplement).

Study quality assessment

The quality assessment for cross-sectional studies showed a low risk of bias (Table 5 supplement) [10, 12, 18, 27, 28, 35, 38, 40, 41, 43].

Cohort studies, based on the NOS scale, can be awarded with a maximum of four, two and three stars for selection, comparability, and outcome sections, respectively. On this basis, all studies had a good quality assessment with scores ranging from 6 to 8 stars (Table 6 supplement) [11, 17, 20–25, 27, 30–32, 34, 36].

The risk of bias for three RCT studies was low according to JBI's checklist [13, 37, 42] (Table 7 supplement).

Discussion

This systematic review provides a comprehensive description of the outcomes of patients with AE-IPF treated with corticosteroids.

Our data show a high short- (i.e., in-hospital and 90-day) and long-term (1-year) mortality of patients with AE-IPF treated with corticosteroids.

Interestingly, patients treated with lower steroid doses and with a background antifibrotic therapy show the lowest short-term mortality rate.

Corticosteroids are the therapeutic cornerstone for exacerbated IPF, despite randomized controlled trials showed no long-term benefits in case of stable disease [2, 4, 8, 48]. International guidelines suggested a high dose (up to 1 g daily) of methylprednisolone but the recommendation was based on small, uncontrolled case series

[2, 8]. A recent survey found that high-dose methylprednisolone or equivalent followed by a slow tapering was the most prescribed pharmacological approach, whereas only one third of respondents usually prescribe lower doses (i.e., 1 mg/kg per day) [9].

A lower in-hospital and 90-day mortality can be achieved in patients treated with 500-1,000 mg/day (i.e., 10 mg/Kg/day) if compared with those treated with 1,000 mg/day, with the highest survival rate in those treated with a starting dose of 1 mg/Kg/day up to 500 mg daily [10, 20, 39].

Unfortunately, it is unclear whether different steroid doses were chosen based on the exacerbation severity.

Farrand et al. did not show a survival benefit in patients with AE-IPF treated with corticosteroids VS. those treated with supportive care alone [10]. However, patients treated with steroids had a pre-admission lower functional impairment and were more likely to require ICU-level care and mechanical ventilation during hospitalization [10].

A recent systematic review found a reduced 90-day mortality in patients with exacerbated, non-IPF, ILD treated with high-dose corticosteroid therapy (> 1 mg/Kg prednisolone) and inconsistent benefits in those with AE-IPF [49].

Our systematic review shows that patients with a background antifibrotic therapy had a lower 90-day mortality than those without.

Antifibrotic therapy may prevent exacerbations. Nintedanib may reduce the time to the first exacerbation when compared to placebo [6]. A recent systematic review of clinical trials and observational studies showed that antifibrotics may reduce the risk of AE in patients with IPF [7]. Our data confirmed small, uncontrolled studies which showed a survival benefit in patients treated with background antifibrotic therapy following an acute exacerbation [50].

Increased risk of death and hospitalization was previously observed in patients with IPF who were treated with a combination of prednisone, immunosuppressants, and N-Acetylcysteine [48].

However, several studies described the concomitant administration of corticosteroids with immunosuppressants during exacerbations, with cyclosporin A and cyclophosphamide being the most prescribed [12, 13, 17, 22–26, 29–38, 44].

Patients treated with immunosuppressants and corticosteroids show better in-hospital and 90-days survival than those with only steroids. However, a randomized controlled trial demonstrated that intravenous cyclophosphamide pulses and high-dose glucocorticoids increased 3-month mortality [13]. These findings highlight the need for high-quality studies to find the most effective pharmacological options.

Antibiotics are commonly prescribed in AE-IPF since bacterial infections may not be confidently ruled out in many patients but no studies have specifically confirmed their usefulness.

This review has several limitations. The findings are mostly based on small observational studies, and most of them had a retrospective epidemiological design, increasing the risk of selection bias. Furthermore, different definitions of IPF and AE were used and different background therapies were described.

Some patients were treated with corticosteroids and immunosuppressive/anti-inflammatory drugs but data to assess 1-year mortality could not be separately obtained in some cases. Thus, the related pooled results should be cautiously interpreted.

Our review failed to retrieve sufficient data to compare outcomes in patients treated with corticosteroids according to the severity of the exacerbation and in those with idiopathic VS. secondary disease.

Based on studies' data no conclusions can be drawn on the association between clinical outcomes and concomitant background antifibrotic therapy and/or immunosuppressive agents and steroid dosages.

In conclusion, our study shows a high short- and long-term mortality in patients with AE-IPF treated with corticosteroids. Lower steroid doses and background antifibrotic therapy might reduce short-term mortality.

Two randomized controlled trials are underway comparing the efficacy of high-dose corticosteroids with placebo and higher VS. lower doses of steroids (Clinicaltrials.gov identifiers: NCT05674994 and NCT04996303). They could provide robust data on the efficacy of this therapy in the treatment of this devastating complication.

High-quality studies are needed to assess whether antibiotics and/or concomitant therapies with anti-inflammatory activity might be associated with a survival benefit.

Larger prospective studies should confirm the role of antifibrotic therapy in improving outcomes in patients surviving an acute exacerbation.

Abbreviations

IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
AE-IPF	Acute exacerbation of idiopathic pulmonary fibrosis
JBJ	Joanna Briggs Institute Critical Appraisal tools
RCT	Randomized controlled trial
CI	Confidence interval
PMX-HP	Polymyxin-B hemoperfusion
HFNC	High-flow nasal cannula
NIMV	Non-invasive mechanical ventilation
IMV	Invasive mechanical ventilation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
MM: conception and design; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted. CA: conception and design and acquisition of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted.MVP: analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted.GN: acquisition of data; drafting the manuscript; revising it critically for important intellectual content; final approval of the version to be submitted.JC: acquisition of data; revising it critically for important intellectual content; final approval of theversion to be submitted.NM: analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be submitted.CT: acquisition of data; revising it critically for important intellectual content; final approval of theversion to be submitted. LAB: acquisition of data; revising it critically for important intellectual content; final approval of theversion to be submitted.GF: acquisition of data; revising it critically for important intellectual content; final approval of the version to be submitted.MZ: acquisition of data; revising it critically for important intellectual content; final approval of theversion to be submitted.GS: conception and design and analysis and interpretation of data; revising it critically for important intellectual content; final approval of the version to be submitted.

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all data generated or analysed during this study are included in this published article.

Declarations

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