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Prognosis of combined pulmonary fibrosis and emphysema: comparison with idiopathic pulmonary fibrosis alone

Chun-guo Jiang, Qiang Fu and Chun-ming Zheng

Abstract

Background: Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome characterized by the coexistence of upper lobe emphysema and lower lobe fibrosis. However, whether CPFE has a higher or lower mortality than idiopathic pulmonary fibrosis (IPF) alone is still not clear. In this study we conducted a meta-analysis to assess the survival rate (SR) of CPFE *versus* IPF alone in clinical trials.

Methods: We performed a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials for trials published prior to 31 March 2018. Extracts from the literature were analyzed with Review Manager version 5.3.

Results: Thirteen eligible trials were included in this analysis (involving 1710 participants). Overall, the pooled results revealed that no statistically significant difference was detected in the 1-year [relative risk (RR) = 0.98, 95% confidence interval (CI): 0.94–1.03, $p = 0.47$], 3-year (RR = 0.83, 95% CI: 0.68–1.01, $p = 0.06$), and 5-year (RR = 0.80, 95% CI: 0.59–1.07, $p = 0.14$) SRs of CPFE *versus* IPF alone.

Conclusions: CPFE exhibits a very poor prognosis, similar to IPF alone. Additional studies are needed to provide more convincing data to investigate the natural history and outcome of patients with CPFE in comparison to IPF.

The reviews of this paper are available via the supplemental material section.

Keywords: combined pulmonary fibrosis and emphysema, idiopathic pulmonary fibrosis, meta-analysis, survival rate

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Correspondence to:
Chun-guo Jiang
Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital, Capital Medical University, 8 Gongti Nanlu, Chaoyang District, Beijing 100020, China
jiang_cg@163.com

Qiang Fu
Department of Internal Medicine, Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Chun-ming Zheng
Medical Research Center, Beijing Institute of Respiratory Diseases, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Introduction

The characteristics of combined pulmonary fibrosis and emphysema (CPFE) is the combination of pulmonary emphysema in the upper lobes and fibrosis mainly in the lower lobes. A series of eight patients with combined emphysema and pulmonary fibrosis on chest computed tomography (CT) was initially described by Wiggins and colleagues.[1] Cottin and colleagues first described the phrase CPFE by conducting a retrospective study that contained 61 patients with emphysema in the upper lobes and diffuse pulmonary fibrosis in the lower lobes on chest CT.[2] CPFE has been described both in patients with idiopathic pulmonary fibrosis (IPF) and in other forms of pulmonary fibrosis. CPFE is characterized by a history of heavy smoking, exertional dyspnea, preserved pulmonary volume, and reduced diffusion capacity, and occurs predominantly in men. High-resolution computed tomography (HRCT) plays a pivotal role in diagnosis. Just as with IPF, CPFE can also frequently cause lots of complications, such as pulmonary arterial hypertension, lung cancer, and acute lung injury.[3]

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic interstitial lung disease of unknown cause. In the absence of lung transplantation, the 3-year and 5-year mortality rates have been reported to

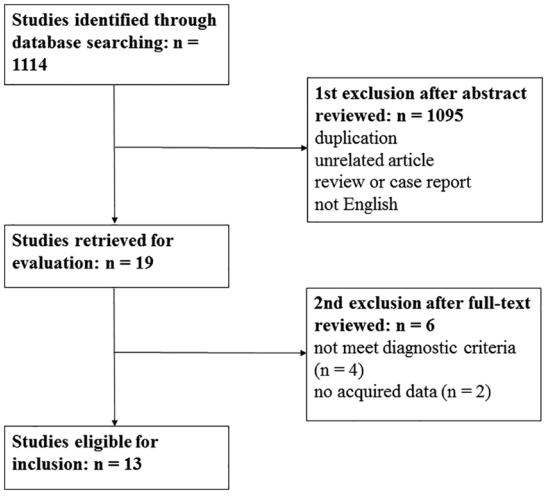

Figure 1. Flow diagram of the study selection process in the meta-analysis.

be approximately 50% and 80%, respectively.[4,5] Compared with other chronic lung fibrotic diseases, IPF appears to have the worst prognosis. CPFE also has a poor prognosis, with a survival time of 2.1–8.5 years after diagnosis,[3] while the median survival of 5 years is reported to range from 35% to 80%.[2,6] However, in the existing literature, the effect of CPFE on survival rate is abhorrent and it is still not clear whether CPFE has a lower or higher mortality than IPF alone. In this study we conducted a meta-analysis of available published literature to assess the survival rate (SR) of CPFE *versus* IPF alone in clinical trials.

Methods

Search strategy

We performed systematic searches of the medical literature for articles published in electronic databases including PubMed, Embase, and the Cochrane central register of controlled trials prior to 31 March 2018 according to a standardized protocol. Search terms were 'emphysema' and 'idiopathic pulmonary fibrosis'. In addition, the reference lists of all the relevant studies and reviews were also checked by hand.

Study selection

Two reviewers (CJ and QF) independently evaluated the inclusion and exclusion criteria, and references for eligibility were determined by both reviewers. Disagreements were resolved by consensus. Eligibility criteria were as follows: (1) studies evaluating CPFE *versus* IPF; (2) articles that provided relevant survival data, Kaplan–Meier survival curves, or both. Studies presenting insufficient data were excluded as were duplicates, non-English studies, conference abstracts, editorials, reviews, case reports, or small case series (less than five patients).

Data extraction and quality assessment

Data were systematically extracted from the selected studies and entered onto a data extraction form designed before beginning the study. Trial characteristics including first author, publication year, country, the sample size, proportion of male patients, mean age of included patients, meaning of CPFE, duration of follow-up, and SRs at 1 year, 3 years, and 5 years were recorded to allow for exploration of potential reasons for any heterogeneity detected between trial results. If possible, the raw value for the survival rate was recorded. When these rates were unavailable, the survival rates were estimated from survival curves. No attempt was made to include unpublished data. The methodological qualities of the eligible studies were evaluated with the Newcastle Ottawa Quality Assessment Scale (NOS).[7] NOS scores of 0–3, 4–6, and 7–9 were considered to indicate low, moderate, and high quality, respectively.

Data synthesis and analysis

The data were analyzed using Review Manager (version 5.3) software by the Cochrane Collaboration (Oxford, England). As primary outcomes, the variances of 1-year, 3-year, and 5-year SRs of CPFE *versus* IPF alone were expressed as a combined relative risk (RR) with a 95% confidence interval (CI). When the p value of the χ^2 test was more than 0.05 or I^2 was less than 50%, the fixed-effect model weighted by the Mantel–Haenszel method was used. Otherwise, the random effect model was applied in the case of significant heterogeneity. A $p < 0.05$ was considered statistically significant.

Results

Study identification

The process of identifying eligible studies is schematically illustrated in Figure 1. A total of 1114 citations from the initial search were found, of which 19 studies were retrieved for further assessment after title and abstract evaluation. Among

Table 1. Characteristics of included trials.

Study	Location	Group	Sample size, *n*	Male	Age (years)	Duration of follow-up on survival (years)	NOS
Mejía *et al.*[8]	Mexico	CPFE IPF alone	31 79	30 49	67 ± 7 63 ± 10	6.6	9
Akagi *et al.*[9]	Japan	CPFE IPF alone	26 33	23 22	65.1 ± 8.5 66.5 ± 9.2	15	9
Kurashima *et al.*[10]	Japan	CPFE IPF alone	129 233	NA NA	NA NA	10	8
Ryerson *et al.*[11]	USA	CPFE IPF alone	29 336	20 239	69.9 ± 8.7 69.0 ± 8.6	8	9
Ye *et al.*[12]	China	CPFE IPF alone	70 55	68 38	64 ± 9 66 ± 8	4	8
Sugino *et al.*[13]	Japan	CPFE IPF alone	46 62	43 46	71.4 ± 6.7 73.7 ± 6.3	8	9
Kim *et al.*[14]	Korea	CPFE IPF alone	26 42	23 24	67.6 ± 2.2 68.2 ± 1.7	11.5	9
Sato *et al.*[15]	Japan	CPFE IPF alone	55 45	53 38	71.8 ± 7.3 69.9 ± 7.1	5	9
Zhang *et al.*[16]	China	CPFE IPF alone	87 105	76 66	66 ± 8.5 60 ± 4.3	5	8
Sato *et al.*[17]	Japan	CPFE IPF alone	12 5	NA NA	NA NA	3.5	7
Papaioannou *et al.*[18]	Greece	CPFE IPF alone	29 62	26 43	75 72	1	8
Kohashi *et al.*[19]	Japan	CPFE IPF alone	34 13	NA NA	NA NA	6.8	9
Portillo *et al.*[20]	Spain	CPFE IPF alone	29 37	29 26	71 ± 7 72 ± 10	10.5	9

Data are mean ± standard error of the mean.
CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; *n*, number of pairwise comparisons; NOS, Newcastle Ottawa Quality Assessment Scale.

these papers, four that compared CPFE and pulmonary fibrosis and two that lacked extractable survivable data were excluded. Ultimately, 13 publications met the inclusion criteria and were included in the meta-analysis.[8–20]

Detailed characteristics of the included trials are shown in Table 1. The 13 studies contained a total of 1710 participants (603 in the CPFE group and 1107 in the IPF alone group) published between 2009 and 2017. Two of the trials were conducted in Europe,[18,20] two in North America,[8,11] and the remaining nine trials in east Asia.[9,10,12–17,19] The number of participants in each study ranged from 17 to 365 individuals. The proportion of male patients varied between 69% and 100% in the CPFE group, and between 57% and 74% in the IPF alone group. The mean age of individuals ranged from 64.0 to 75.0 years in the CPFE group, and from 60.0 to 73.7 years in the IPF alone group. The duration of follow-up on survival was between 1 and 15 years. The NOS was used to evaluate the quality of the selected studies. All studies were graded as high quality, with scores ranging from 7 to 9 (Table 1).

1-year SR comparison of CPFE versus IPF alone

Twelve trials reported the 1-year SR comparison of CPFE *versus* IPF alone.[8–15,17–20] There were no statistically significant differences in the 1-year SR between the CPFE group and the IPF alone group (RR = 0.98, 95% CI: 0.94–1.03, $p = 0.47$). Heterogeneity was not evident, as assessed by the statistics ($I^2 = 19\%$, $p = 0.26$) (Figure 2).

3-year SR comparison of CPFE versus IPF alone

Eleven trials reported the 3-year SR comparison of CPFE *versus* IPF alone.[8–15,17,19,20] Statistically significant differences in the 3-year SR between the CPFE group and the IPF alone group were not observed (RR = 0.83, 95% CI: 0.68–1.01, $p = 0.06$). Heterogeneity was substantial, as assessed by the statistics ($I^2 = 77\%$, $p < 0.00001$) (Figure 3).

5-year SR comparison of CPFE versus IPF alone

Ten trials reported the 5-year SR comparison of CPFE *versus* IPF alone.[8–11,13–16,19,20] The combined results of the trials revealed that the CPFE group had no significant differences in the 5-year SR compared with the IPF alone group (RR = 0.80, 95% CI: 0.59–1.07, $p = 0.14$). Heterogeneity was substantial, as assessed by the statistics ($I^2 = 79\%$, $p < 0.00001$) (Figure 4).

Publication bias

The funnel plots for publication bias appeared to be symmetrical (Figure 5). These results indicated no evidence of publication bias for 1-year, 3-year, and 5-year SRs compared with the IPF alone group.

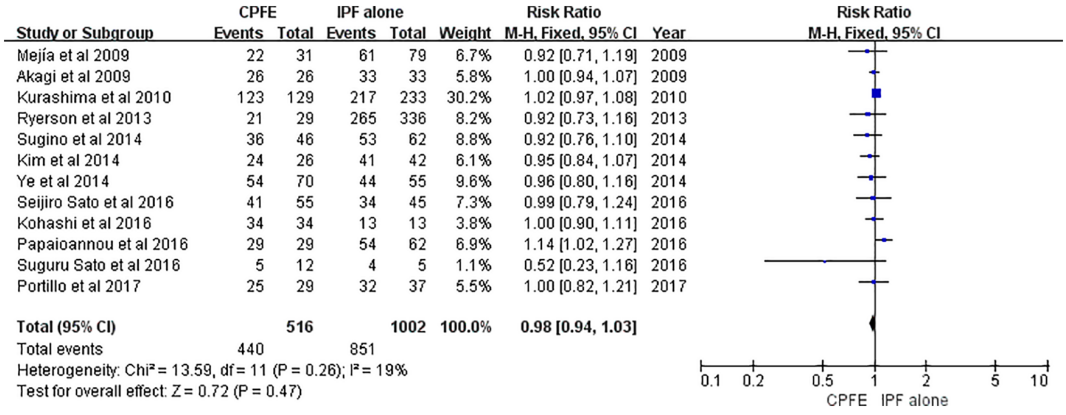

Figure 2. Forest plot of trials of CPFE *versus* IPF alone on relative risk of 1-year SR.
CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis.

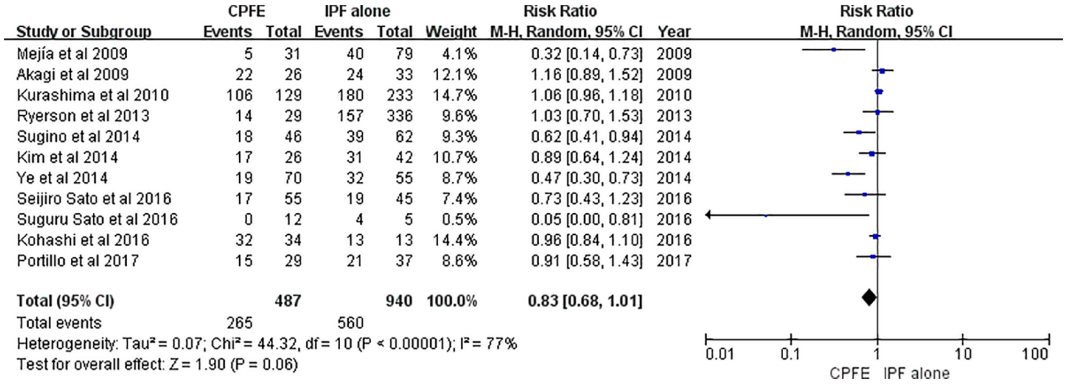

Figure 3. Forest plot of trials of CPFE *versus* IPF alone on relative risk of 3-year SR.
CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis.

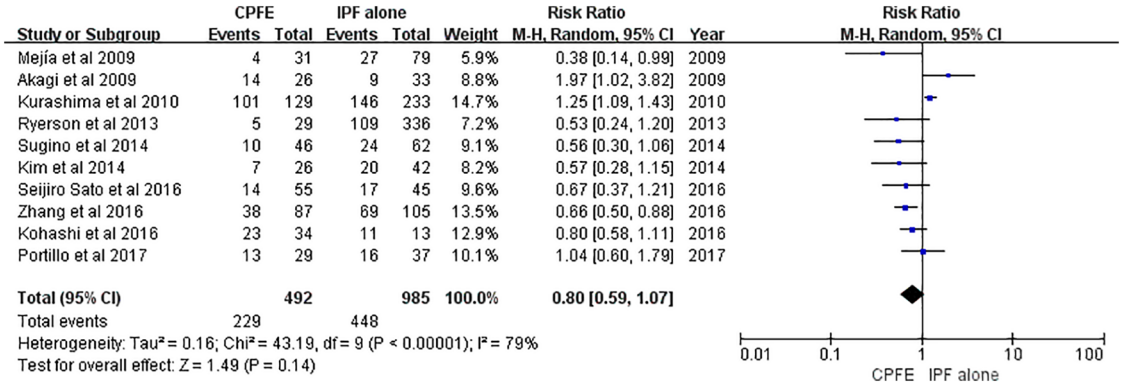

Figure 4. Forest plot of trials of CPFE *versus* IPF alone on relative risk of 5-year SR.
CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis.

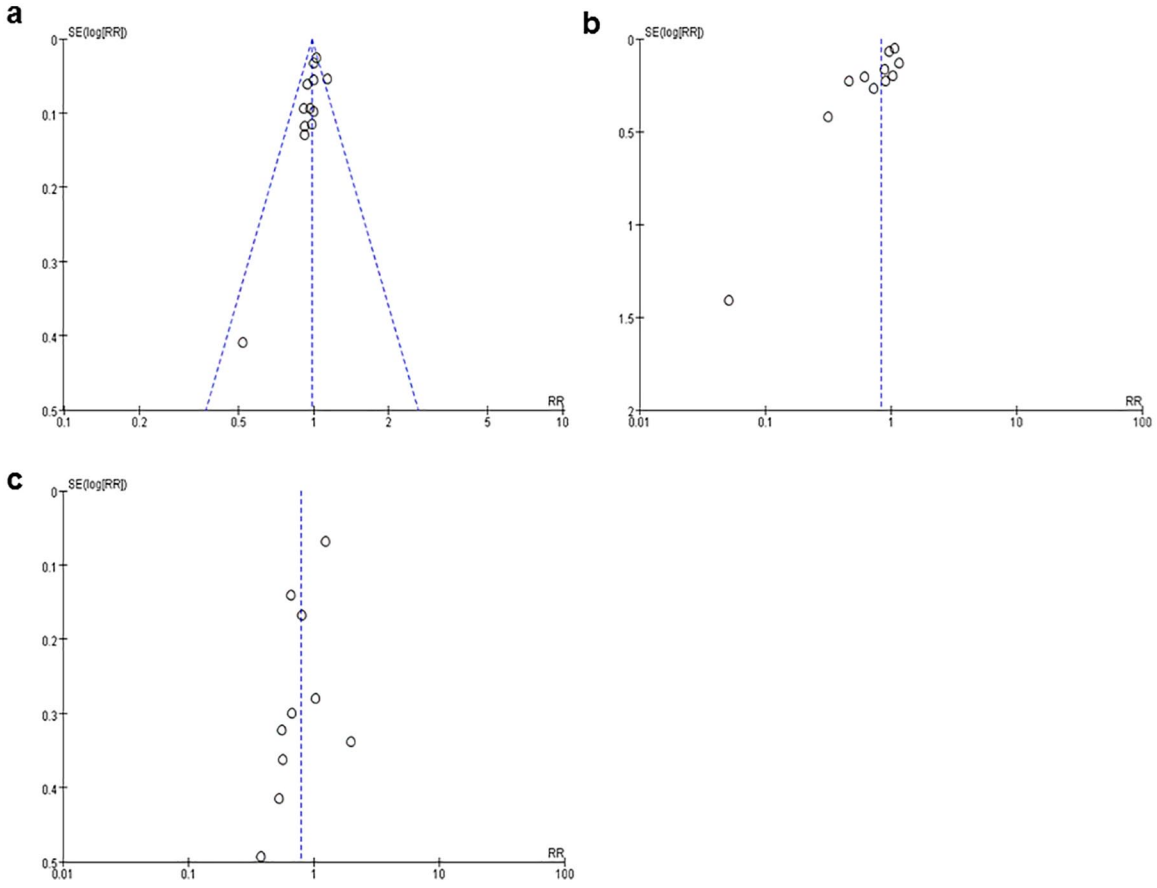

Figure 5. Funnel plot to assess for evidence of publication bias. (a) Funnel plot for the studies on 1-year SR; (b) Funnel plot for the studies on 3-year SR; (c) Funnel plot for the studies on 5-year SR.

Discussion

To our knowledge, this is the first meta-analysis to examine the prognosis of CPFE *versus* IPF alone. There is no statistically significant difference in the 1-year, 3-year, and 5-year SRs of CPFE *versus* IPF alone in this meta-analysis. The results indicate that the mortality of patients with CPFE is similar to those with sole IPF.

Sharing common pathogenetic mechanisms of cigarette exposure and genetic susceptibility, IPF often coexists with emphysema.[21] Compared with sole IPF, the coexistence of IPF and emphysema leads to relatively preserved lung volume and markedly impaired diffusion capacity. The conflicting results were obtained from single studies based on whether the presence of emphysema affects mortality for patients with pulmonary fibrosis. It is reported by Mejía and colleagues that the survival of patients with isolated IPF is better than those with CPFE.[8] Sugino and colleagues also reported similar findings.[13] Conversely, some reports have found no significant difference in mortality.[11] Kurashima and colleagues described a worse survival in patients with IPF which made things even more complex.[10] The reasons for these conflicting findings may include the relative proportion of IPF pathology in patients in the CPFE group, the type and extent of clinically meaningful emphysema,[21] the retrospective nature of the studies, different enrollment criteria, and control group selection. Our meta-analysis has reduced the level of controversy to a certain extent.

Several limitations of this study should not be ignored. These results may include publication bias, as the number of studies analyzed was still small, although it has provided data from more than 1700 patients. Furthermore, the heterogeneous patient populations (i.e. different causes of pulmonary fibrosis showing various natural history) may represent a variety of prognoses because of imprecise definitions of CPFE. In our meta-analysis, almost all CPFE patients in the articles we adopted were compliant with IPF diagnostics, the outcomes of which may be worse than the widely defined CPFE. Finally, a subgroup analysis of controlling for confounders was not conducted because of a lack of stratified data reported in the trials.

Conclusion

This meta-analysis shows that CPFE has a very poor prognosis, similar to IPF alone. However, additional studies are needed in order to provide more convincing data to investigate the natural history and outcome of patients with CPFE in comparison to IPF.

Author contributions

CJ, QF, and CZ contributed equally to this study. QF contributed to data collection, analysis, and interpretation, and preparation of the manuscript. CZ designed the study, contributed to the introduction, and reviewed/edited the manuscript. CJ served as the guarantor of the paper, and takes responsibility for the integrity of the work as a whole, from inception to published article. All authors read and approved the final manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Chun-guo Jiang https://orcid.org/0000-0003-4577-7529

Supplemental material

The reviews of this paper are available via the supplemental material section.

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