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Guideline

Japanese guidelines for the treatment of idiopathic pulmonary fibrosis 2023:Revised edition☆

Masashi Bando [a,*], Sakae Homma [b], Hiroshi Date [c], Kazuma Kishi [b], Hiroyoshi Yamauchi [a], Susumu Sakamoto [b], Atsushi Miyamoto [d], Yoshihito Goto [e], Takeo Nakayama [f], Arata Azuma [g,h], Yasuhiro Kondoh [i], Takeshi Johkoh [j], Yasuhiko Nishioka [k], Junya Fukuoka [l], Yasunari Miyazaki [m], Ichiro Yoshino [n,o], Takafumi Suda [p], on behalf of the Ministry of Health, Labour and Welfare, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/ Research on Intractable Diseases, and Japanese Respiratory Society

[a] *Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan*
[b] *Department of Respiratory Medicine, Toho University Omori Medical Center, 6-11-1 Omori-nishi, Ota-ku, Tokyo, 143-8541, Japan*
[c] *Department of Thoracic Surgery, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan*
[d] *Department of Respiratory Medicine, Respiratory Center, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470, Japan*
[e] *Clinical Research Center, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto, Kyoto, 612-8555, Japan*
[f] *Department of Health Informatics, Graduate School of Medicine and School of Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto, Kyoto, 606-8501, Japan*
[g] *Pulmonary Medicine, Tokorozawa Mihara General Hospital, 2-2934-3 Mihara-cho, Tokorozawa-shi, Saitama, 359-0045, Japan*
[h] *Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan*
[i] *Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi, 489-8642, Japan*
[j] *Department of Radiology, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo, 660-8511, Japan*
[k] *Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima, 770-8503, Japan*
[l] *Department of Pathology Informatics, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan*
[m] *Department of Respiratory Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan*
[n] *Department of Thoracic Surgery, International University of Health and Welfare Narita Hospital, 852 Hatakeda, Narita City, Chiba, 286-8520, Japan*
[o] *Department of General Thoracic Surgery, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8677, Japan*
[p] *Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatus, 431-3192, Japan*

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with a poor prognosis and an unknown cause that generally progresses to pulmonary fibrosis and leads to irreversible tissue alteration. The "Guidelines for the treatment of idiopathic pulmonary fibrosis 2017," specializing in the treatment of IPF for the first time in Japan and presenting evidence-based standard treatment methods suited to the state of affairs in Japan, was published in 2017, in line with the 2014 version of "Formulation procedure for Minds Clinical Practice Guidelines."

Because new evidence had accumulated, we formulated the "Guidelines for the treatment of Idiopathic Pulmonary Fibrosis 2023 (revised 2nd edition)." While keeping the revision consistent with the ATS/ERS/JRS/ALAT IPF treatment guidelines, new clinical questions (CQs) on pulmonary hypertension were added to the chronic stage, in addition to acute exacerbation and comorbid lung cancer, which greatly affect the prognosis but are not described in the ATS/ERS/JRS/ALAT IPF guidelines. Regarding the advanced stages, we additionally created expert consensus-based advice for palliative care and lung transplantation. The number of CQs increased from 17 in the first edition to 24. It is important that these guidelines be used not only by respiratory specialists but also by general practitioners, patients, and their families; therefore, we plan to revise them appropriately in line with ever-advancing medical progress.

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* Corresponding author. 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan.
E-mail address: bando034@jichi.ac.jp (M. Bando).

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Author contributions

Contributor Homma S was creation committee chairperson. Bando M, Date H and Suda T were the member of supervisory committee. Goto Y and Nakayama T were guideline creation expert. Kishi K, Azuma A, Kondoh Y, Johkoh T, Nishioka Y, Fukuoka J, Miyazaki Y and Yoshino I were the member of panel committee. Yamauchi H, Sakamoto S and Miyamoto A were guidelines secretariats. All authors contributed to the writing of the final manuscript.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) has the poorest prognosis among idiopathic interstitial pneumonias (IIPs), with no established standard treatment. With respect to the treatment of IPF, an international consensus statement [1] concerning the diagnosis and treatment of IPF was internationally published in 2000, mainly led by ATS, with several randomized controlled trials having been conducted since then. Based on these results, ATS/ERS/JRS/ALAT first published evidence-based guidelines for the diagnosis and management of IPF [2] in 2011. Because further evidence was subsequently accumulated, the Clinical Practice Guidelines [3] regarding the treatment of IPF were updated in 2015.

In Japan, the “Guidelines for the treatment of Idiopathic Pulmonary Fibrosis 2017” [4] was formulated in 2017, with the aim of complying with the international treatment guidelines mentioned above and presenting treatment and management methods that match the actual state of affairs in Japan. New clinical questions (CQs) were set, along with the existing CQs, and literature searches as well as systematic reviews of newly created evidence were conducted in order to formulate the “Guidelines for the treatment of Idiopathic Pulmonary Fibrosis 2023 (revised 2nd edition).”

The main purpose of this guideline is to outline rational treatment methods and treatments for patients based on a proper diagnosis of IPF. However, these guidelines only present the strength of recommendations based on the GRADE system and do not impede the physician’s discretionary powers, considering the benefits and disadvantages to their patients. Additionally, it should be clearly stated that it is not intended to contribute to decision making in medical disputes or complaints. In clinical practice, it is important for the attending physician to make the final decision upon consultation with the patient and to provide sufficient explanation to the patient and record it in their medical chart.

1.1. Users of the guidelines

Users of this guideline are not only physicians who specialize in respiratory disease but also non-specialist physicians, medical staff, patients, families, and supporters.

2. Methods

2.1. Committee composition

The IPF treatment guideline is a guideline specifically addressing treatment and management which was created with the collaboration of the Japanese Respiratory Society (JRS) under the leadership of the Ministry of Health, Labour and Welfare, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases. “The Manual for the Diagnosis and Treatment of Idiopathic Interstitial Pneumonias” was jointly published in 2004 in Japan by the JRS and the Ministry of Health, Labour and Welfare, the Study Group on Diffuse Pulmonary Disorders, as a book to support decision-making in the clinical setting of IIPs including IPF, with a revised fourth edition published in 2022. Internationally, the ATS/ERS reported an international consensus statement on IPF in 2000, and in 2011, the ATS/ERS/JRS/ALAT formulated evidence-based guidelines for the diagnosis and management of IPF, the most recent version of which was published in 2022, after several revisions. Based on the above background, the members of the research team on diffuse lung disease became members of the formulation committee, and experts in drafting clinical practice guidelines were requested to join them. The formulation committee included 48 members, consisting of a supervisory committee, clinical guideline formulation method experts, formulation committee members (including clinical guideline panel members and review authors), a systematic review team, and cooperating committee members. The guideline management committee decided on important clinical issues, set CQs for each, and decided on outcomes, which were the components of the CQs. The systematic review team systematically reviewed the evidence for the determined CQs, and clinical practice guideline panel members made recommendations. Other formulation committee members were in charge of areas unsuitable for systematic reviews, which often exist in IPF clinical settings, wrote review guidelines, and made general adjustments.

2.2. Guideline formulation procedure

The formulation began in January 2020, and at the 1st General Committee meeting, the revision policy was determined while CQ and outcome proposals were considered, important clinical issues, outcomes, and CQs were examined at the first panel meeting to make the final decision. There were 24 CQs sets. The formulation committee began reviewing, selecting, and making formulation recommendations for each CQ in May 2021, and by December 2021, the systematic review team proposed draft recommendations for 22 CQs. For the two CQs, it was considered difficult to make recommendations based on the literature; therefore, they were treated as expert advice. In response to this proposal, the formulation committee held meetings to determine the strength of the recommendations on January 23, 30, and April 29, 2022, to decide on the draft of the final recommendations. Since it was difficult for patients to participate in the panel meetings, the draft reflected the results of research conducted on patients (1189 in total) who participated in an interstitial pneumonia/pulmonary fibrosis study group, sponsored by the New Strategic Research Group to Build Evidence for Diffuse Lung Disease, Expenses for Practical Research Project for Intractable Disease, and Commissioned Research and Development of Japan Agency for Medical Research and Development. Upon completion of the panel meetings, based on their results, the formulation committee began to revise the recommendations and supplementary explanations according to the GRADE system. The first manuscript was completed by the end of October 2022. A supervisory committee meeting was held in November 2022, when the entire manuscript was reviewed and revised by the supervisory committee. After the evaluation of the manuscript by the evaluation committee and public comments were solicited using the website of the Japanese Respiratory Society in late November 2022, the manuscript was revised from December 2022 to January 2023 based on external evaluations and public comments. Subsequently, the manuscript was proofread for the first and second editions, printed, bound, and published in April 2023.

2.3. Selection of important clinical issues

During the formulation of the previous edition, a questionnaire survey was conducted among the members of the research team on diffuse lung disease, with three issues selected as important clinical subjects: " treatment in the chronic stage, treatment during acute exacerbation, and "Treatment of IP-complicated lung cancer, including IPF." Upon revision, new important clinical issues CQs were solicited on the website of the JRS, and we examined new CQ proposals and outcome proposals at the 1st supervisory committee meeting in January 2020, after which the final decision was made at the 1st panel meeting in March. In addition to the three subjects in the previous edition,

"Treatment in the advanced stage'' and "Treatment of IP-complicated pulmonary hypertension'' were added as important clinical subjects in this revised edition.

2.4. Extraction of outcomes

Extraction of outcomes and assessment of their importance were conducted in January 2020, considering the components of the CQ. Outcomes were given to each important clinical subject, a score was assigned to assess the degree of importance, and the opinions of all panel meeting participants were aggregated using the modified Delphi method. The assessment of importance is based on the "Minds clinical practice guideline formulation manual 2020'' and was scored from 1 to 9 (7–9: important for decision making; 4 to 6: important but not critical for decision making; and 1 to 3: not important to patients), with items selected as critical (7–9 points) adopted as outcomes.

2.5. Formulating clinical questions

The AGREE II instrument, which is widely used worldwide as an evaluation method for clinical practice guidelines, requires that "the health issues addressed by the guidelines be specifically described'' as evaluation items. In recent clinical practice guidelines, the PICO format used in EBM [what kind of patient, what should be done (intervention), compared with others (comparison), what kind of outcome and how will it turn out (outcome)] is commonly used to specify CQ. In accordance with this policy and based on discussions within the formulation committee, 24 CQs were finally formulated in these guidelines, with a systematic review of existing literature conducted for 22 of these CQs.

2.6. Literature review and preparation of evidence profiles

The databases used were PubMed, the Cochrane Library, and Ichushi, with the periods covered by the literature search being 1946–2020, 1994–2020, and 1997–2020, respectively. For existing CQs, the period was set from 2015 to 2020. The target language was English or Japanese, while the research design favored randomized controlled trial. In case there was little or no thereon, we expanded the literature search to include non-randomized controlled trials, as clinical trials with a comparison group, and cohort studies as observational studies with a comparison group. In the event, nothing was found therein; case series without a comparison group were also included. A literature search was conducted for each CQ, and the titles and abstracts of the obtained literature, as a result of the electronic search, were checked in accordance with the above policy, and the literature confirming the text was determined.

We extracted summaries of individual studies that were considered important in making recommendations for each CQ. Because the literature with a comparison group, including randomized controlled trials, was very limited overall, when summarizing the evidence as a whole, it was difficult to display it in the form of a quantitative Summary of Findings (SoF), which is recommended in the "GRADE System for Clinical Practice Guidelines" and "Minds Clinical Practice Guideline Development Manual 2020," we focused on creating a descriptive summary.

When deciding on recommendations at panel meetings, taking into consideration the results of the above work, a consensus on recommendations was comprehensively formed from the perspectives of the overall quality (strength) of the evidence for important outcomes, the balance between benefits and harms, and the patient's values, intentions, wishes, cost, and available resources. In the process, the Evidence to Decision (EtD) table was used as needed to help resolve problems.

The number of specialists in this disease is extremely limited; therefore, if the formulators are limited by the same COI criteria as for the clinical practice guidelines for ordinary diseases, there is a concern that the experience and knowledge of the specialists will not be fully reflected in the clinical practice guidelines. From the point of view of the relevant member's expertise, the COI status was disclosed to maintain fairness, and the member was asked to participate in the discussion and recommendation decisions by acknowledging their own bias and refraining from making remarks.

2.7. External review process

Prior to the release of these guidelines, opinions were collected from members and directors of the society, and the entire draft was evaluated externally. The international standard guideline evaluation tool AGREE II was used for this external evaluation. The AGREE II consists of differential items consisting of 23 items in six domains, along with an overall evaluation. Each item was scored on a scale of 1–7, with an area-specific score calculated for each area. Comments from evaluators were reflected as much as possible in these guidelines. Comments that cannot be reflected are considered in the next update. We will consider partial revisions or the next revision as necessary, even after publication, upon receiving feedback from users through the Society's website.

3. The GRADE system and self-assessment

The quality of evidence and terminology used for the recommendations are presented in Tables 1 and 2. This guideline presents recommended statements in response to each Clinical Question (CQ) and denotes the strength of the recommendation and the certainty of the overall evidence. (Ex: **1A** = Strong recommendation based on high-quality of evidence. **2D** = Week recommendation based on very low-quality of evidence.) The self-assessment of these clinical practice guidelines formulated using the GRADE system is shown in Table 3.

Since its announcement in 2004, the GRADE system has been methodologically refined through the accumulation of experiences and discussions by various stakeholders worldwide, and the core parts thereof are being established. As of today, it can be said that the above-mentioned six criteria have been clearly demonstrated as a result. Although the GRADE working group positions these requirements as essential, the creation of a standardized evidence profile is not necessarily required, as seen in criterion 4. Additionally, it is not required to have a division of labor between the systematic review team and the panel that decides the recommendations, or consensus building by an interdisciplinary panel that also includes patients, which was emphasized in the US Institute of Medicine's report "Clinical Practice Guidelines We Can Trust" (2011). The "Evidence to Decision (EtD) Frameworks," which was also referred to when making recommendations in these guidelines, is a useful and interesting tool, but the use thereof is not required at this moment. However, it is also listed in the Minds Manual and is expected to become more popular in the future. Although the GRADE system has pioneered the frontline of clinical practice guideline formulation methods, it is still in the process of development, and it can be said that there are issues and uncertain areas, regarded as the goal for which to strive as well as the core part.

Formulating the guidelines using the GRADE system for the treatment of PF, which is an intractable disease designated by the Ministry of Health, Labor, and Welfare with limited clinical evidence of a sufficient scale and high quality, was a major challenge for clinicians, as was the case in the past. However, there is no doubt that efforts to incorporate

Table 1
Quality of evidence.

Quality of evidence	
High	A
Moderate	B
Low	C
Very low	D

Table 2
Interpretation of strong and weak recommendations.

Strength of recommendation		
Strong recommendation	Recommend that it should (not) be used	1
Week recommendation	Suggest that it should (not) be used	2

such an advanced and broad-ranging clinical practice guideline formulation method will lead to a reconsideration of clinical decision making, along with the direction of clinical research for diseases that require a high degree of expertise. It is expected that the methods of Minds2020 and these guidelines, which are oriented toward the GRADE system, will be used as a starting point for improving IPF patient care, building a clinical system, and promoting clinical research.

Table 3
Self-assessment for Japanese guidelines for the treatment of IPF 2023.

1. The certainty of evidence (strength of evidence/reliability of effect estimates) uses the same definition as the GRADE working group. → Satisfactory
2. Each GRADE domain is explicitly considered to assess the certainty of the evidence.
3. The overall certainty of the evidence should be rated in three or four categories (e.g., high, moderate, low, and very low) consistent with the GRADE working group definitions for each important outcome. → Satisfactory
4. Evidence summaries and evidence-based decision criteria are used as the basis for decisions that determine the certainty of evidence and the strength of recommendations. Ideally, evidence profiles based on systematic reviews should be used to assess the certainty of evidence. At the very least, the evidence that was evaluated and the method of identification and evaluation of the evidence should be specified. → Meeting minimum requirements.
5. The direction, strength, or decision of a recommendation was made by explicitly considering each GRADE criterion. Ideally, the reviewed evidence, additional considerations, and judgments should be left as transparent documents using GRADE's evidence to determine frameworks. → Satisfactory overall.
6. It is desirable that the strength of the recommendation be evaluated using the same definitions as the GRADE working group (the terminology may differ), such as two categories (for or against the option) and strong, weak, or conditional → satisfactory.

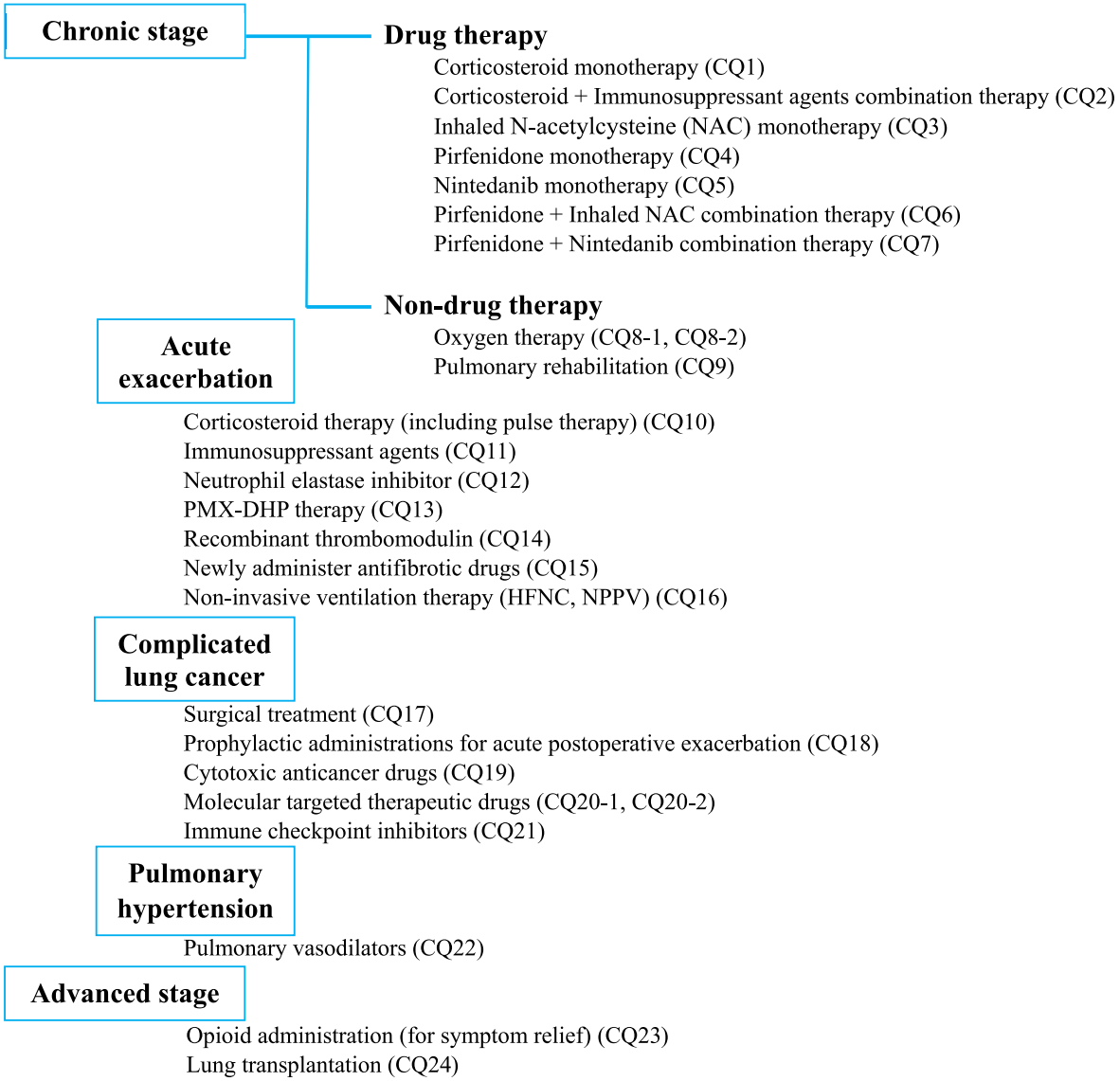

Fig. 1. Clinical questions for the treatment of IPF.

4. Recommendations for specific treatment questions

Fig. 1 shows clinical questions for treatment of IPF.

Supplemental table shows a comparison of changes from the first edition (2017 edition).

5. Clinical questions CQ1-24

5.1. CQ1

Should corticosteroid monotherapy be used for patients with IPF?

We recommend not administering corticosteroid monotherapy to patients with IPF in the chronic stage.

1 D (Very low)

5.1.1. Conclusion

Even after the first edition, no study has reported on the efficacy of steroid monotherapy. Therefore, based on the evidence outlined in the 2017 guidelines [4], the guideline formulation committee recommends not administering corticosteroid monotherapy to patients with IPF in the chronic stage (strength of recommendation 1, quality of evidence D).

5.2. CQ2

Should combination therapy of corticosteroids and immunosuppressant be used for patients with IPF?

We recommend not administering combination therapy with corticosteroids and immunosuppressant agents to patients with IPF in the chronic stage.

1 C (Low)

5.2.1. Conclusion

Even after the first edition, no large-scale studies have conclusively demonstrated the efficacy of combination therapy with steroids and immunosuppressants.

Therefore, based on the evidence outlined in the 2017 guidelines [4], the guideline formulation committee recommends not administering combination therapy with corticosteroids and immunosuppressant agents to patients with IPF in the chronic stage (strength of recommendation 1, quality of evidence C).

5.3. CQ3

Should inhaled N-acetylcysteine monotherapy be used for patients with IPF?

We suggest not administering inhaled NAC monotherapy to patients with IPF in the chronic stage.

2 C (Low)

5.3.1. Conclusion

Since the first edition, no studies have reported the effectiveness of NAC inhalation monotherapy. Therefore, based on the evidence outlined in the 2017 guidelines [4], the guideline formulation committee suggests not administering inhaled NAC monotherapy to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence C).

5.3.1.1. Notes. NAC inhalation therapy for IPF is a treatment unique to Japan, with evidence of monotherapy reported only in Japan. Only two randomized controlled trials were included: the number of patients was small and the studies were conducted in an open-label manner; therefore, the reliability of the evidence regarding the clinical question is low, and the usefulness of NAC inhalation monotherapy has not been demonstrated. It has been shown that oral NAC therapy may be effective for IPF patients with the TT genotype, which is a minor allele of the TOLLIP gene (rs3750920) [5], so going forward, it is hoped that clinical research will be conducted to identify the phenotypes for which NAC inhalation therapy is effective.

5.4. CQ4

Should pirfenidone be used for patients with IPF?

We suggest administering pirfenidone monotherapy to patients with IPF in the chronic stage.

2 B (Moderate)

5.4.1. Conclusion

Since the first edition, no randomized controlled trial comparing pirfenidone alone with placebo has been reported. Therefore, based on the evidence outlined in the 2017 guidelines [4], the guideline formulation committee suggests administering pirfenidone monotherapy to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence B).

5.5. CQ5

Should nintedanib be used for patients with IPF?

We suggest administering nintedanib monotherapy to patients with IPF in the chronic stage.

2 B (Moderate)

5.5.1. Conclusion

Since the first edition, no randomized controlled trials comparing nintedanib alone and placebo have been reported. Therefore, based on the evidence outlined in the 2017 guidelines [4], the guideline formulation committee suggests administering nintedanib monotherapy to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence B).

5.6. CQ6

Should combination therapy of pirfenidone and inhaled N-acetylcysteine be used for patients with IPF?

We suggest not administering combination therapy with pirfenidone and inhaled NAC to patients with IPF in the chronic stage.

2 B (Moderate)

5.6.1. Evidence summary

A Japanese phase III study on the combination therapy of pirfenidone and NAC inhalation [6]. This is an open-label phase III randomized controlled trial conducted at multiple institutions in Japan that targeted 81 patients with IPF (41 patients in the pirfenidone + NAC combination group and 40 patients in the pirfenidone alone group), mainly led by a research team on diffuse lung disease in Japan [6]. The primary endpoint, FVC decline over 48 weeks, was worse in the NAC combination group than in the pirfenidone alone group (−300 mL vs. −123 mL, $p = 0.018$), with no significant difference in mortality rate. (1/34, 3% vs. 3/36, 8%, relative risk 0.35, $p = 0.33$).

5.6.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering combination therapy with pirfenidone and inhaled NAC to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence B).

5.7. CQ7

Should combination therapy of pirfenidone and nintedanib be used for patients with IPF?

We suggest not administering combination therapy with pirfenidone and nintedanib to patients with IPF in the chronic stage.

2 D (Very low)

5.7.1. Evidence summary

Although there are three randomized controlled trials concerning the combination treatment of nintedanib and pirfenidone, a single-arm prospective study, and two retrospective observational studies [7–12], the primary endpoints of most of these papers are safety, tolerability, or pharmacokinetics/pharmacodynamics (PK/PD).

Ogura et al. [7] conducted a randomized controlled trial on 50 Japanese patients with IPF and found that the incidence of adverse events was 10 out of 21 patients (47.6%) in the nintedanib and pirfenidone combination group (hereinafter referred to as the two-drug combination group), and there was no difference between 9 out of 17 patients (52.9%) in the nintedanib alone group, and all symptoms were mild to moderate, with gastrointestinal disorders being the most common. Permanent discontinuation occurred in 4 of the 50 patients (8%), with no tendency to increase in the two-drug combination group. It was found that the steady-state blood concentrations of nintedanib and its metabolites tended to decrease in the combination group.

The INJOURNEY study [8] was an open-label randomized controlled trial that analyzed the effects of adding 2400 mg/day pirfenidone to 104 IPF patients with FVC ≥50% who were able to receive 300 mg/day nintedanib for 4–5 weeks. Although gastrointestinal disorders as an adverse event after 12 weeks, which was the primary endpoint, tended to be more common in the two-drug combination group (37 of 53 patients (69.8%) and in the nintedanib alone group (27 of 51 patients (52.9%)], other adverse events and serious adverse events did not increase in the two-drug combination group. The concomitant use of pirfenidone had no effect on the blood concentration of nintedanib.

Richeldi et al. conducted a randomized controlled trial with 37 patients with IPF and pharmacokinetics as primary endpoint [9]. The results demonstrated that there was no difference in the pharmacokinetics. The safety observation period was 28 days, with 3 patients (15%) in Group 1 (single-drug group) who discontinued the drug due to adverse events and none in Group 2 (two-drug combination group).

Flaherty et al. conducted a single-arm phase IV study to evaluate the safety and tolerability of combination therapy in 89 patients with IPF by administering pirfenidone (1602 to 2403 mg/day) alone for 23–71 days after obtaining informed patient consent, followed by nintedanib (200–300 mg/day) for 24 weeks [10]. Thirteen patients (15%) discontinued treatment because of treatment-emergent adverse events (TEAEs). Diarrhea, nausea, or vomiting were common among the TEAEs observed in 74 patients (83%); however, serious adverse events were observed in only 2 patients (2%).

Hisata et al. reported a multicenter retrospective observational study of 46 Japanese patients with IPF treated with a two-drug combination therapy. The primary endpoint was adverse events [11]. During the average observation period (59 weeks), 33 patients (71.7%) developed some type of adverse event, whereas 14 patients (30.4%) required discontinuation of one or both drugs. Although the most common adverse events were anorexia (18 cases, 39.1%) and diarrhea (16 cases, 34.8%), only two cases (4.3%) had serious adverse events. There were more cases of Japanese severity classification grade III or IV in the drug discontinuation group than in the non-discontinuation group (90.9% vs. 61.1%, $p = 0.0129$).

Although the survival rate was not the primary endpoint in the five studies mentioned above, there were no deaths in the target group during the observation period in the analysis of adverse events.

A U.K. single-center retrospective study by Noor et al. observed 161 patients with IPF (24 patients with pirfenidone alone, 14.9%; 86 patients with nintedanib alone, 53.4%; 18 patients with a two-drug combination group, 11.2%; and 33 patients with no treatment, 20.5%) for 36 months [12]. The annual FVC decline was similar in the pirfenidone alone, nintedanib alone, and no treatment groups (139 mL, 131 mL vs. 158.1 mL) and was significantly worse in the two-drug combination group (233 mL) than in the other groups. ($p = 0.01$). The permanent discontinuation rates were 5 patients (27.8%) in the two-drug combination group, 5 patients (21%) in the pirfenidone alone group, and 18 patients (21%) in the nintedanib alone group.

5.7.1.1. Conclusion. As mentioned above, the adverse event profile of the combination of pirfenidone and nintedanib in patients with IPF is consistent with the data for each drug, suggesting that changes in safety, tolerability, and pharmacokinetics due to this combination may be manageable. However, there is insufficient evidence regarding its therapeutic effects. Based on the above evidence, the guideline formulation committee suggests not administering combination therapy with pirfenidone and nintedanib to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence D).

5.8. CQ8-1

Should oxygen therapy be used for IPF patients with hypoxemia?

We recommend administering oxygen therapy to patients with IPF associated with resting hypoxemia in the chronic stage.

1 D (Very low)

5.8.1. Conclusion

Because there is no evidence that oxygen therapy improves survival rates for IPF patients with hypoxemia, the recommended level was determined based on evidence and expert opinion for patients with chronic obstructive pulmonary disease. Based on the above evidence, the guideline formulation committee recommends administering oxygen therapy to patients with IPF associated with resting hypoxemia in the chronic stage (strength of recommendation 1, quality of evidence D).

5.8.1.1. Notes. There is no evidence that oxygen therapy improves survival rates in patients with IPF. However, we determined that oxygen therapy is recommended for IPF patients with resting hypoxemia, considering data from chronic obstructive pulmonary disease.

5.9. CQ8-2

Should oxygen therapy be used for IPF patients with exertional hypoxemia?

We suggest administering oxygen therapy to patients with IPF associated with exertional hypoxemia in the chronic stage.

2 C (Low)

5.9.1. Evidence summary

Three randomized controlled trials investigated the effectiveness of oxygen therapy for fibrotic interstitial pneumonia, including IPF with exertional hypoxemia.

Dowman et al. [13] from Australia conducted a randomized crossover trial involving 11 patients with IPF. Inhaling 50% oxygen while using an ergometer increased exercise tolerance time by an average of 99 s (425 s → 524 s, $p = 0.002$) compared to the non-oxygenated group, with the Borg breathlessness scale improving by 1 (4 → 3, $p = 0.02$).

Visca et al. [14] conducted a randomized crossover study in 76 patients with fibrotic interstitial pneumonia who had no resting hypoxemia but had hypoxemia during a 6-min walk. The difference between the two-week oxygen therapy group and the non-oxygen therapy group was 18.5 m (95% CI 10.9 to 26.1, $p = 0.001$) in terms of the 6-min walking distance, and 3.7 (95% CI 1.8 to 5.6, $p < 0.0001$) for the total score of K-BILD, which is an index of QOL, while the shortness of breath score, UCSDSOBQ, was −8.0 (95% CI -12.4 to −3.6, $p < 0.0001$), all of which improved with oxygen therapy.

Khor et al. [15] conducted a triple-blind, mock-controlled study on 24 patients with fibrotic interstitial pneumonia and hypoxemia using a 6-min walk test. There was no significant difference in the 6-min walking distance and shortness of breath in the group receiving oxygen during exercise for 12 weeks compared to the non-administered group; however, the psychological domain of the LCQ was 0.9 (95% CI 0.2 to 1.6, p = 0.01) higher, suggesting an improvement in cough-related QOL.

The above three clinical studies indicate that oxygen therapy has the potential to improve exercise tolerance and quality of life related to shortness of breath and coughing in patients with fibrotic interstitial pneumonia with exertional hypoxemia.

5.9.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering oxygen therapy to patients with IPF associated with exertional hypoxemia in the chronic stage (strength of recommendation 2, quality of evidence C).

5.9.1.1.1. Notes. There is no evidence that oxygen therapy improves the survival of IPF patients. In IPF patients with exertional hypoxemia, oxygen therapy tends to improve exercise tolerance, coughing, and shortness of breath.

5.10. CQ9

Should pulmonary rehabilitation be used for patients with IPF?

We suggest administering pulmonary rehabilitation to patients with IPF in the chronic stage.

2 B (Moderate)

5.10.1. Evidence summary

According to the 2021 Cochrane Review [16], there were 21 randomized controlled trials (including only abstracts) on the effectiveness of pulmonary rehabilitation for interstitial lung disease (ILD), with IPF as the target disease in 9 trials [17–25] and various ILDs in seven trials. Of the seven trials targeting various ILDs, stratified analyses targeting IPF were conducted in two trials [26,27]. The results of the meta-analysis of studies targeting patients were as follows. Eight randomized controlled trials [17–22,26,27] were able to evaluate the 6-min walking distance, with the 6-min walking distance increasing by an average of 37.25 m (95% CI 26.16–48.33) during the 3- to 12-week follow-up period. This value exceeded the minimum important difference (MID) of 29–34 m for the 6-min walking distance in IPF. Four randomized controlled trials [17,18,26,27] were able to assess shortness of breath, the score of which decreased by an average of 0.41 points (95% CI 0.74 to 0.09) over a follow-up period of 8–12 weeks. Six randomized controlled trials [17–19,23,25,27] were able to evaluate QOL using the SGRQ, with the total score decreasing by an average of 7.91 points (95% CI 5.26–10.55) over a follow-up period of 8 weeks to 6 months. The above results indicate that pulmonary rehabilitation has the potential to improve short-term exercise tolerance and shortness of breath after implementation, as well as QOL in patients with IPF. However, the long-term effects beyond six months were not clear. Additionally, the mortality rate could be evaluated in three randomized controlled trials [17,26,27], with the odds ratio (OR) for the intervention group after 6–11 months being 0.32 (95% CI 0.08 · 1.19), indicating no significant difference. There have been no reports of side effects related to pulmonary rehabilitation.

5.10.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering pulmonary rehabilitation to patients with IPF in the chronic stage (strength of recommendation 2, quality of evidence B).

5.11. CQ10

Should corticosteroids including pulse therapy be used for patients with acute exacerbation of IPF?

We suggest administering corticosteroid therapy including pulse therapy to patients with an acute exacerbation of IPF, however, this therapy may not be a reasonable option for some patients.

2 D (Very low)

5.11.1. Evidence summary

Although high-dose steroids are often used to treat acute exacerbation of IPF, no randomized controlled trials have been conducted to date to verify their effectiveness. In a retrospective analysis of 102 cases of acute exacerbation of IPF, Hozumi et al. reported that steroid pulse therapy followed by steroid maintenance therapy was performed in 46 cases, with a 90-day survival rate of 84.8 % after acute exacerbation [28].

On the other hand, although this was a retrospective analysis of a small number of cases, have found no benefit to steroid therapy. Farrand et al. [29] performed a retrospective analysis of 82 cases of acute exacerbation of IPF (37 and 45 patients in the steroid and non-steroid treatment groups, respectively) to evaluate the effect of steroid treatment on in-hospital mortality [29]. No significant relationship was found between steroid administration and in-hospital death (p = 0.74), with the overall survival rate adjusted for artificial ventilation management, ICU admission, Charlson comorbidity index, and prehospital respiratory function significantly lower in the steroid-treated group than in the non-steroid-treated group (p = 0.019).

5.11.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering corticosteroid therapy including pulse therapy to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence D), however, this therapy may not be a reasonable option for some patients.

5.11.1.1.1. Notes. However, it is difficult to provide specific recommendations regarding the dose, route, and duration of steroid therapy.

5.12. CQ11

Should immunosuppressant agents be used for patients with acute exacerbation of IPF?

We suggest not administering immunosuppressant agents to patients with an acute exacerbation of IPF, however, this therapy may be a reasonable option for some patients.

2 C (Low)

5.12.1. Evidence summary

Because high-dose steroids are often used in the treatment of acute exacerbations of IPF, immunosuppressive agents are sometimes given as concomitant therapy with steroid therapy, and the immunosuppressive agents used in combination with steroids vary. However, no randomized controlled trials have been reported by January 2021, the period covered by the literature search for this systematic review.

In a retrospective analysis using the Japanese DPC database, there was no significant difference in in-hospital mortality between 384 patients who received cyclosporine A in combination with steroid therapy and 7605 patients who did not receive cyclosporine A [30].

Regarding cyclophosphamide, no significant difference was found in the 90-day survival rate (p = 0.70) or cumulative survival rate (p = 0.57) in a study comparing steroid and cyclophosphamide pulse combination therapy with steroid monotherapy using propensity score matching [28]. Furthermore, in a retrospective study comparing survivors and those who died after acute exacerbation of IPF, univariate

analysis found that the concomitant use of cyclophosphamide pulse therapy was not significantly associated with survival (p = 0.07). Furthermore, in a study that retrospectively analyzed patients with acute exacerbation of IPF who underwent endotracheal intubation using the Diagnosis Procedure Combination (DPC) database in Japan, no significant difference was observed in the in-hospital mortality rate between 104 patients who underwent cyclophosphamide pulse therapy in combination with steroid therapy and 1734 patients who did not [31].

5.12.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering immunosuppressant agents to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence C), however, this therapy may be a reasonable option for some patients.

5.12.1.1.1. Notes. The first randomized controlled trial on combination therapy with immunosuppressants for acute exacerbation of IPF was reported in September 2021, which falls outside the period covered by this systematic review. The 3-month overall mortality rate in the high-dose steroid therapy plus cyclophosphamide pulse therapy group (CY group) was 45%, whereas it was 31% (p = 0.10) in the placebo group (steroid therapy alone group) [32]. The addition of cyclophosphamide pulse therapy had no effect on reducing mortality, with the 3-month mortality rate tending to be higher in the CY group than in the placebo group. The results of this study are described in the notes because they suggest that the mortality rate may increase when combined with cyclophosphamide pulse therapy.

5.13. CQ12

Should neutrophil elastase inhibitors be used for patients with acute exacerbation of IPF?

We suggest not administering neutrophil elastase inhibitors to patients with an acute exacerbation of IPF.

2 D (Very low)

5.13.1. Conclusion

Because there have been no studies verifying efficacy for an acute exacerbation of IPF since the first edition was published in 2017, the guideline formulation committee suggests not administering neutrophil elastase inhibitors (SSH) to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence C).

5.14. CQ13

Should PMX therapy be used for patients with acute exacerbation of IPF?

We suggest not administering PMX-DHP therapy to patients with an acute exacerbation of IPF, however, this therapy may be a reasonable option for some patients.

2 C (Low)

5.14.1. Evidence summary

No randomized controlled trials on this treatment were found. Six studies were included in this review, only three of which were retrospective observational studies that limited the subject to acute exacerbation of IPF and compared a PMX-DHP treatment intervention group with a non-intervention group [33–35]. These three retrospective observational studies were all from the same single institution with a small number of cases; therefore, although the results suggested the effectiveness of PMX-DHP, careful consideration is necessary.

5.14.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering PMX-DHP therapy to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence C), however, this therapy may be a reasonable option for some patients.

5.14.1.1.1. Notes. There are no randomized controlled trials; therefore, the committee cannot make a strong recommendation at this time.

The results of the remaining three studies examining the efficacy of PMX-DHP for interstitial pneumonia, including IPF, are shown. Komaki et al. [36] showed improved 28- and 90-day survival rates and improved PaO2/FiO2 (P/F) ratios following intervention in the implementation group (5 out of 6 patients with IPF) and in the non-implementation group (10 out of 15 patients with IPF). Furusawa et al. [37] showed no significant difference in survival rate between the implementation group (10 out of 24 cases with IPF) and the non-implementation group (14 out of 30 cases with IPF); however, there was a significant improvement in the P/F ratio. Furthermore, Ichiyasu et al. [38] reported the 90-day mortality rate in patients with IPF and acute exacerbation as 60 % with implementation group vs 57.1 % with non-implementation group.

Based on these results, this treatment may be a reasonable option for a small number of patients; therefore, subsequent randomized controlled trials would be warranted. Equipment is required to perform PMX-DHP; therefore, the implementation of this treatment is limited.

5.15. CQ14

Should recombinant thrombomodulin be used for patients with acute exacerbation of IPF?

We suggest not administering recombinant thrombomodulin to patients with an acute exacerbation of IPF.

2 B (Moderate)

5.15.1. Evidence summary

With respect to this treatment for acute exacerbation of IPF, a multicenter phase III placebo-controlled randomized controlled trial was conducted in Japan, and the results were reported by Kondoh et al., in 2020 [39]. The 90-day survival rates were 72.5% in the rTM group and 89.2% in the placebo group, indicating no benefit (p = 0.0863).

5.15.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering recombinant thrombomodulin to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence B).

5.16. CQ15

Should newly antifibrotic drugs be started for patients with acute exacerbation of IPF?

We suggest not administering new antifibrotic drugs to patients with an acute exacerbation of IPF.

2 D (Very low)

5.16.1. Evidence summary

There are no randomized controlled trials for either pirfenidone or nintedanib and only two retrospective cohort studies on pirfenidone.

5.16.1.1. Pirfenidone. Although there have been no randomized controlled trials, two retrospective case-control studies have been reported. Furuya et al. investigated the difference in survival rates between pirfenidone and pirfenidone in 47 patients with acute exacerbation of IPF [40]. The survival rate after three months was 55% in the pirfenidone combination group and 34% in the non-combination group in all cases, which was a significant difference. Of the 22 patients treated with recombinant thrombomodulin, univariate analysis showed that the 3-month survival was good in those treated with pirfenidone.

However, pirfenidone was administered before acute exacerbation in half of these cases; therefore, the effectiveness of the new administration is unclear. Matsumura et al. investigated the difference in prognosis depending on the presence or absence of new pirfenidone administration after acute exacerbation in 31 cases of acute exacerbation of interstitial lung disease including IPF [41]. Pirfenidone was concomitantly used in 14 patients and was not concomitantly used in 17 patients, with treatment initiated after acute exacerbation in all cases. There were no significant differences in 30-day (78.6% vs. 64.7%, p = 0.46) and 90-day survival rates (64.3% vs. 52.9%, p = 0.72) between the two groups. Regarding serum indicators, there were significant differences in white blood cell counts (difference between days 1 and 7 and 14) and serum CRP levels (difference between days 1 and 7) in the pirfenidone group. There was no significant difference in the pattern of HRCT findings between the two groups.

5.16.1.2. Nintedanib. There are no reports on nintedanib, including randomized controlled trials and retrospective studies.

5.16.1.2.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering new antifibrotic drugs to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence D).

5.17. CQ16

Should high-flow nasal cannula (HFNC) oxygen therapy and noninvasive positive pressure ventilation (NPPV) be used for patients with acute exacerbation of IPF?

We suggest administering noninvasive respiratory support (HFNC and NPPV) to patients with an acute exacerbation of IPF, however, these therapies may not be a reasonable option for some patients.

2 D (Very low)

5.17.1. Evidence summary

No study to compare the efficacy of HFNC/NPPV therapy with oxygen supplementation therapy has been conducted. The only studies included in this review were two retrospective studies with a small number of cases that compared HFNC and NPPV.

Omote [42] et al. conducted a retrospective study comparing 13 patients in the HFNC group and 19 patients in the NPPV group among 32 patients with acute respiratory failure due to IP and found that HFNC improved the 30-day mortality rate with a significant difference on multivariate analysis (odds ratio 0.148, 95% CI, 0.025 to 0.880; p = 0.036). There was no significant difference in intubation rate (8% vs. 37%, p = 0.069). Koyauchi et al. [43] retrospectively investigated 84 patients with respiratory failure due to IP, and found that the 30-day survival and in-hospital mortality rates of HFNC (N = 54) vs NPPV (N = 30) with 31.5% vs. 30.0% and, 79.6% vs. 83.3%, respectively, with no significant difference. The incidence of adverse events was significantly lower in the HFNC group (1.9% and 23.3%, respectively; p = 0.003), however, shortness of breath did not differ before and after the treatment in either the HFNC or NPPV groups. Among the patients who died in the hospital, the HFNC group was significantly able to engage in oral intake until just before death (p = 0.037) and their conversational ability was significantly good (p = 0.042).

5.17.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering noninvasive respiratory support (HFNC and NPPV) to patients with an acute exacerbation of IPF (strength of recommendation 2, quality of evidence D), however, these therapies may not be a reasonable option for some patients.

5.18. CQ17

Should surgical treatment be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest surgical treatment to patients with IP-complicated lung cancer including IPF, however, this treatment may not be a reasonable option for some patients.

2 C (Low)

5.18.1. Evidence summary

5.18.1.1. Regarding postoperative complications. The incidence of postoperative acute exacerbation varies from 0% to 75% [44–50]. The mortality rate following the onset of AE varies from 33.3% to 100% but is still high. Sato et al. reported that the incidence of post-operative AE in patients with NSCLC was 9.3% with a mortality rate of 43.9% [51]. Furthermore, seven independent risk factors were identified: history of acute exacerbation, surgical method, UIP pattern upon imaging, male sex, presence or absence of preoperative steroid treatment, KL-6 level, and %VC. A risk score was proposed [52].

5.18.1.2. Regarding the treatment results. There are limited reports on survival [44,46,53,54]. It should be noted that there are no randomized controlled trials, and the reports were conducted at a single institution and included a small number of patients (21–107 patients), with the exception of 1763 cases by Sato et al. [44]. This report [44] indicated that the 5-year survival rate for all surgically treated NSCLC cases was 40%. Additionally, the 5-year survival rate according to surgical method in Stage IA was 33.2% for partial resection, 61% for segmental resection, and 68.4% for lobectomy. Other reports examining surgical methods and treatment outcomes include single-center retrospective studies [53]. Although the 3-year overall survival rate in this study was 67.1% for lobectomy (50 cases) and 81.9% for segmental or partial resection (57 cases), with no statistically significant difference. In response to this report, a phase III trial of lobectomy versus partial or segmental resection for lung cancers smaller than 4 cm was initiated in 2018 (JCOG1708) [55].

5.18.1.2.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests surgical treatment to patients with IP-complicated lung cancer including IPF (strength of recommendation 2, quality of evidence C), however, this treatment may not be a reasonable option for some patients.

5.19. CQ18

Should prophylactic medications for postoperative acute exacerbation be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest not administering prophylactic medications to prevent a postoperative acute exacerbation to patients with IP-complicated lung cancer including IPF, however, this therapy may be a reasonable option for some patients.

2 C (Low)

5.19.1. Evidence summary

Medications aimed at preventing postoperative acute exacerbation of lung cancer complicated by IP, including IPF, have been reported in a small number of cases, including sivelestat [54,56–58] and pirfenidone [59–61].

Although sivelestat has been reported to have no cases of postoperative acute exacerbation in a small number of cases ranging from 10 to 31 cases [56–58], subsequent retrospective studies did not confirm the efficacy of single agents [47] or in combination with steroids [54].

A retrospective study reported that pirfenidone suppressed acute exacerbation [58]. It has also been reported that acute exacerbation was suppressed in 72 patients in the non-administered group compared to 28 patients in the administered group, under conditions of medium-to high-risk patients [59] 90 days following surgery. Currently, a

multicenter prospective phase III trial is being conducted in Japan, based on a phase II trial that showed efficacy [61].

5.19.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering prophylactic medications to prevent a postoperative acute exacerbation to patients with IP-complicated lung cancer including IPF (strength of recommendation 2, quality of evidence C), however, this therapy may be a reasonable option for some patients.

5.20. CQ19

Should cytotoxic anticancer drugs be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest administering cytotoxic anticancer drugs to patients with IP-complicated lung cancer including IPF, however, this therapy may not be a reasonable option for some patients.

2 C (Low)

5.20.1. Evidence summary

5.20.1.1. First-line treatment for non-small cell lung cancer (prospective study). All of these were single-arm prospective intervention studies. Because there are no studies that have limited their focus to IPF, the results must be interpreted considering that the subject patients differ from study to study.

Kenmotsu et al. [62] investigated the safety and efficacy of carboplatin (CBDCA) + nab-paclitaxel (nab-PTX) therapy for 94 patients with NSCLC complicated by ILD. Acute exacerbation occurred in 4.3% of patients overall, with 6.0% of the 50 patients having a UIP pattern, while ORR was 51%, the median PFS was 6.2 months, and MST was 15.1 months.

Asahina et al. [63] investigated the safety and efficacy of CBDCA + nab-PTX therapy for 36 patients with NSCLC complicated by ILD. Acute exacerbation occurred in 5.6% of patients, ORR was 55.6%, median PFS was 5.3 months, and MST was 15.4 months.

Fukuizumi et al. [64] investigated the safety and efficacy of CBDCA + weekly PTX therapy for 35 patients with NSCLC complicated by IIPs. Acute exacerbation occurred in 12.1% of patients, ORR was 69.7%, median PFS was 6.3 months, and MST was 19.8 months.

Hanibuchi et al. [65] investigated the safety and efficacy of CBDCA + S-1 therapy for 33 patients with NSCLC complicated by ILD. Acute exacerbation occurred in 6.1% of patients, ORR was 33.3%, median PFS was 4.8 months, and MST was 12.8 months.

Sekine et al. [66] investigated the safety and efficacy of CBDCA + S-1 therapy for 21 patients with NSCLC complicated by ILD. Acute exacerbation occurred in 9.5% of patients, ORR was 33%, median PFS was 4.2 months, and MST was 9.7 months.

5.20.1.2. First-line treatment for small cell lung cancer (retrospective study with no restrictions on target disease or regimen). Minegishi et al. [67] examined 120 SCLC patients who underwent chemotherapy among 396 lung cancer patients with IIPs. Acute exacerbation occurred in 3.7% of the 82 patients who underwent CBDCA + VP-16 therapy and 10.5% of the 38 patients who underwent CDDP + VP-16 therapy.

Nishiyama et al. [68] investigated 27 patients with SCLC who underwent chemotherapy among 105 patients with lung cancer complicated by ILD. Acute exacerbation occurred in 13.6% of the 22 patients who underwent CBDCA + VP-16 therapy.

Akaike et al. [69] investigated 16 patients with SCLC complicated by ILD who underwent chemotherapy. Platinum plus VP-16 therapy was administered to 16 patients, with acute exacerbation occurring in 31.3% of patients. The ORR was 50.0%, the median PFS was 184 days, and the MST was 236 days.

5.20.1.3. Second line treatment. Regarding the second line treatment of lung cancer complicated by ILD, there have been no prospective studies, and only retrospective studies have been reported. There have been some reports that the frequency of acute exacerbations is the same or increases with the primary treatment. Watanabe et al. [70] investigated 35 patients with NSCLC complicated by IP who underwent DOC as the second line treatment, following platinum-combined chemotherapy as the initial treatment. Acute exacerbation occurred in 14.3% of the patients. ORR was 8.6%, DCR was 37.1%, median PFS was 1.6 months, and MST was 5.1 months. S-1 was reported to cause relatively few acute exacerbations, with the frequency of acute exacerbations ranging from 0 to 4.2% [71,72].

While there have been reports of PTX-containing regimens [73], topotecan [74] and PTX-containing regimens and topotecan [75] as secondary treatments for SCLC complicated by ILD, the frequency of acute exacerbation is relatively high in all cases, ranging from 13.0 to 29.4%.

Minegishi et al. [67] examined 278 cases of lung cancer complicated by IIPs that underwent second line treatment. Acute exacerbation was observed in 16.2% of the patients. For NSCLC, the ORR was 7.4%, the DCR was 40.7%, and the median survival from second line therapy was 8.0 months. For SCLC, the ORR was 25.7%, the DCR was 48.6%, and the median survival time after second line treatment was 8.7 months.

5.20.1.4. Risk factors of acute exacerbation. Although there are various retrospective reports regarding the risk factors for acute exacerbation, there is currently no consensus. Reported risk factors for acute exacerbation using image analysis include the SUV value of interstitial lesions in the contralateral lung on FDG-PET [76] and the GGA score on HRCT [10,77]. There have been reports of low FVC values [78] and UIP patterns [79], regarding risk factors for acute exacerbation using baseline patient characteristics, blood test values, and respiratory function test values. Furthermore, Isobe et al. [80] conducted a study using a risk score using a comprehensive anticancer drug score, calculated from the frequency of past acute exacerbations, smoking history, immunosuppressive drug administration history, steroid drug administration history, and %DLco. They reported that a score of $\geq$6 was associated with an increased risk of acute exacerbation.

5.20.1.4.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering cytotoxic anticancer drugs to patients with IP-complicated lung cancer including IPF (strength of recommendation 2, quality of evidence C), however, this therapy may not be a reasonable option for some patients because of the risk of severe drug-induced lung injury (acute exacerbation), such as that associated with chemotherapy, is considered to be higher than in lung cancer without IP.

5.21. CQ20-1

Should molecular-targeted therapeutic drugs involved in angiogenesis inhibition be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest administering molecular-targeted therapeutic drugs to patients with IP-complicated lung cancer including IPF, however, this therapy may not be a reasonable option for some patients.

2 D (Very low)

5.21.1. Evidence summary

No randomized controlled trials have been conducted on molecular targeted drugs for advanced stage lung cancer complicated by ILD, including IPF. Two reports provided a retrospective review of the combined use of an antibody preparation (bevacizumab) against vascular endothelial growth factor (VEGF).

Hamada et al. evaluated the efficacy and safety of chemotherapy for advanced non-squamous non-small cell lung cancer with existing ILD by

dividing patients into groups with and without bevacizumab [81]. In this study, while there were no acute exacerbations in the bevacizumab combination group, acute exacerbation occurred in seven of 31 cases (22.5%) in the non-combination group, suggesting that combination bevacizumab may suppress acute ILD exacerbation. Progression-free survival was significantly longer in the combination group; however, there was no significant difference in overall survival. Shimizu et al. investigated the safety and efficacy of carboplatin + paclitaxel therapy with or without bevacizumab in patients with advanced non-squamous non-small cell lung cancer complicated by ILD [82]. Although this study indicated that progression-free survival tended to be longer in the combination group, there was no significant difference in overall survival between the two groups. There was only one case (10%) of ILD exacerbation in the combination group, with no significant difference.

5.21.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests administering molecular-targeted therapeutic drugs involved in angiogenesis inhibition to patients with IP-complicated lung cancer including IPF, while taking into account the clinical results of NSCLC without ILD (strength of recommendation 2, quality of evidence C), however, this therapy may not be a reasonable option for some patients because of the risk of severe drug-induced lung injury (acute exacerbation), as chemotherapy is considered to be higher than in lung cancer without IP.

5.21.1.1.1. Notes. Outside the literature search period of these guidelines, Otsubo et al. reported the results of the world's first randomized phase III trial (J-SONIC trial), which evaluated the safety and efficacy of combining nintedanib with cytotoxic anticancer drugs in untreated NSCLC complicated by IPF in Japan [83]. In this trial, patients were assigned in a 1:1 ratio to the nintedanib + carboplatin + nab-paclitaxel group (nintedanib + chemotherapy group) and the carboplatin + nab-paclitaxel treatment group (chemotherapy group). There was no significant difference in the event-free survival between the two groups, which was the primary endpoint. It was confirmed that the combination of antifibrotic drugs and cytotoxic anticancer drugs was relatively safe. While progression-free survival for non-small cell lung cancer was significantly longer in the nintedanib plus chemotherapy group than in the chemotherapy group, the overall survival was not significantly different between the two groups.

5.22. CQ20-2

Should molecular-targeted therapeutic drugs for driver gene mutations be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest or recommend not administering molecular-targeted therapeutic drugs for driver gene mutations to patients with IP-complicated lung cancer including IPF.

At this stage, we cannot draw any conclusions regarding the strength of the recommendations. D (Very low)

5.22.1. Evidence summary

Although it is not clear whether IPF is included, there have been three reports of EGFR-TKIs targeting ILD. Although there were no papers meeting the criteria for a systematic review, the following papers were listed as non-selected papers for reference only.

Kudoh et al. prospectively investigated drug-induced lung injury caused by gefitinib and cytotoxic anticancer drugs in patients with advanced non-small cell lung cancer (NSCLC) [84]. The incidence rates of drug-induced lung injury during the 12-week observation period were 4.0% and 2.1%, respectively. Risk factors for developing drug-induced lung injury include older age, poor performance status, smoking, recent diagnosis of NSCLC, presence of pre-existing ILD, and history of lung resection. Johkoh et al. investigated the risk factors for drug-induced lung injury in a cohort of patients treated with erlotinib [85]. Approximately 3% of patients develop drug-induced lung injury, with a frequency as high as 10.7% in patients with ILD. Minegishi et al. conducted a multicenter study in Japan to investigate the frequency of chemotherapy-induced ILD exacerbation in 278 cases of lung cancer with existing IIPs (including 146 cases with a UIP pattern) [67]. The frequency of ILD exacerbation with gefitinib in the first-line treatment was 83.3%, with an overall exacerbation of 44.4 % with EGFR-TKIs in the second-line treatment, which was high.

5.22.1.1. Conclusion. The voting results of the guideline formulation committee indicated that 75% are for "suggest not administering this drug'', while 25% are for "recommend not administering it.'' Therefore, a consensus that required 80% or more of the votes was not reached. However, because a consensus has been reached on not administering molecular targeted drugs for driver gene mutations to IP-complicated lung cancer, including IPF, the recommendation of this CQ is "suggest or recommend," with no conclusions drawn at this stage regarding the strength of the recommendations.

5.23. CQ21

Should Immune checkpoint Inhibitors be used for patients with comorbid lung cancer in IPF and other IPs?

We suggest not administering checkpoint inhibitors to patients with IP-complicated lung cancer including IPF, however, this therapy may be a reasonable option for some patients.

2 D (Very low)

5.23.1. Evidence summary

5.23.1.1. Prospective study. Regarding the PD-1 inhibitor nivolumab, Fujimoto et al. [86,87] have reported the results of two single-arm prospective studies on previously treated NSCLC complicated by mild interstitial pneumonia. The selection criteria for interstitial pneumonia in either study were as follows: a possible UIP pattern or a pattern inconsistent with the UIP pattern on HRCT, no autoantibodies suggestive of collagen disease, and %VC maintained at 80% or higher. First, no pneumonitis was observed in a pilot study involving six patients. Subsequently, in a phase II study involving 18 patients at four institutions, 11% of patients developed pneumonitis; however, all cases were grade 2 and promptly improved with steroid treatment. These two studies exhibited high efficacy, with a response rate of 39–50% and a disease control rate of 72–100%.

In contrast, a multicenter single-arm phase II study (TORG1936/AMBITIOUS study) of the PD-L1 inhibitor atezolizumab in previously treated NSCLC complicated by IP, reported by Ikeda et al. [88], was canceled after enrolling 17 patients (38 patients were planned) because pneumonitis frequently occurred. The selection criteria for interstitial pneumonia in this study were as follows: a UIP pattern or NSIP pattern on HRCT, no autoantibodies suggestive of collagen disease, and %FVC maintained at 70% or higher. The imaging patterns included UIP in 35%, and honeycomb was observed in 41% patients. Median value of predicted FVC was 85%. The incidence of pneumonitis was 29% for all grades, 24% for Grade 3 or higher, and 6% for Grade 5. Logistic regression analysis suggested that the presence of honeycomb could be a risk factor for pneumonitis.

5.23.1.2. Retrospective study. In a multicenter study of 216 patients with NSCLC who underwent nivolumab monotherapy following second-line treatment, Kanai et al. [89] compared the safety between an IP group (26 patients) and a non-IP group (190 patients). While the incidence of all-grade and grade $\geq$3 pneumonitis was significantly higher in the IP group than in the non-IP group (31% vs. 12% and 19% vs. 5%, respectively), there were no deaths due to pneumonitis.

Furthermore, a study of 123 NSCLC patients treated with a single PD-

1 inhibitor reported by Yamaguchi et al. [90], included 30% of IP complications. In the multivariate logistic regression analysis, 14.6% developed pneumonitis, indicating that the presence or absence of fibrosis on CT was the only risk factor for developing pneumonitis.

A study by Nishiyama et al. [68] of 48 cases of NSCLC complicated by IP treated with anti-PD-1 or PD-L1 inhibitors indicated that 38% had IPF and 19% had a UIP pattern on CT. The frequency of pneumonitis was 15%, and ground-glass attenuation was an independent risk factor for developing pneumonitis.

In contrast, a study of 72 patients with NSCLC with PD-L1 ≥50% who underwent pembrolizumab monotherapy as the first-line treatment reported by Yamaguchi et al. [91], indicating that 14% of the cases were complicated by IP. However, there was no difference in the frequency of pneumonitis between the IP and non-IP groups (20% and 22%, respectively), and no significant difference in overall survival between the two groups.

5.23.1.2.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering checkpoint inhibitors to patients with IP-complicated lung cancer including IPF (strength of recommendation 2, quality of evidence D), however, this therapy may be a reasonable option for some patients.

5.24. CQ22

Should pulmonary vasodilators be used for patients with pulmonary hypertension complicated by IPF?

We suggest not administering pulmonary vasodilators to patients with IPF-complicated pulmonary hypertension, however, this therapy may be a reasonable option for some patients.

2 A (High)

5.24.1. Evidence summary

The effectiveness of pulmonary vasodilators for pulmonary hypertension complicated by interstitial lung disease has not been proven. Three placebo-controlled, multicenter, double-blind studies using bosentan [92], riociguat [93], and pirfenidone + sildenafil [94] showed that efficacy could not be proven or that there were many adverse events; consequently, these drugs are not recommended for the treatment of pulmonary hypertension complicated by interstitial lung disease. Thus, promising results have been reported for inhaled NO, although the number of cases was small [95].

5.24.1.1. Conclusion. Based on the above evidence, the guideline formulation committee suggests not administering pulmonary vasodilators to patients with IPF-complicated pulmonary hypertension (Strength of Recommendation 2, quality of evidence A), however, this therapy may be a reasonable option for some patients.

5.24.1.1.1. Notes. Although outside the period of this literature search, it has been reported that exercise tolerance as assessed by a 6-min walking test was improved in the treprostinil inhalation group compared to the placebo group in a recent multicenter, randomized, double-blind, placebo-controlled trial examining the effects of inhaled treprostinil on pulmonary hypertension complicated by interstitial lung disease. It is anticipated to be a treatment option for pulmonary hypertension complicated by interstitial lung disease [96].

Although CQs 23 and 24 are important clinical issues, randomized controlled trials are ethically difficult and high-level evidence cannot be expected in the future. However, the committee formulating these guidelines believes that it is necessary to provide a certain direction to support the judgment of clinical practitioners, and so has decided to present the guidelines as an expert consensus. It should be noted that while advice based on expert consensus is not a term commonly used in clinical practice guidelines, it has been carefully designed and presented as advice to clinical practitioners from experienced experts based on the characteristics of CQ and limited evidence.

5.25. CQ23

Should opioids be used for dyspnea in patients with IPF?

Advice based on expert consensus.

We advise that careful attention should be paid to the indications, efficacy evaluation, and measures to prevent any side effects before drug use.

5.25.1. Background

Dyspnea is one of the most excruciating symptoms in patients with advanced-stage IPF; therefore, alleviation of dyspnea symptoms is extremely important. Systemic administration of morphine is recommended for dyspnea in cancer patients according to the "Guidelines for relieving respiratory symptoms in cancer patients" [97] and the American Society of Clinical Oncology (ASCO) guidelines [98]. Additionally, the usefulness of systemic morphine administration in relieving dyspnea symptoms has been reported in non-cancerous respiratory diseases such as interstitial lung disease (ILD) and COPD [99–101]. Systemic morphine is often used in clinical practice to relieve symptoms of terminal respiratory distress in IPF patients.

5.25.1.1. Explanation. Matsuda et al. retrospectively investigated the usefulness of continuous subcutaneous injection of morphine for dyspnea in end-stage patients with idiopathic IIPs and reported that the numerical rating scale (NRS) for dyspnea was significantly reduced by continuous subcutaneous injection of morphine 4 h after administration compared to before administration [102]. Furthermore, Matsuda et al. conducted a prospective phase I study of subcutaneous injection of morphine for dyspnea and reported the tolerability of a single 2 mg dose of morphine [103].

Currow et al. conducted a phase II dose escalation study that initiated the administration of a once-daily sustained-release formulation of morphine to 10 mg/day in patients with chronic dyspnea (83 cases, including 10 ILD patients) presenting with mMRC 3 or 4; if no effect was found, the dose was increased by 10 mg–30 mg/day [99]. As a result, 52 of 83 patients (62%) showed improvement of 10% or more in the dyspnea VAS, with approximately 70% of the patients receiving morphine at a dose of 10 mg/day of sustained-release morphine.

Krong-White et al. conducted a prospective placebo-controlled study to verify the effectiveness of one-week oral administration of immediate-release morphine 20 mg/day (5 mg at a time, 4 times a day) in 36 patients with fibrotic ILD (including 17 IPF patients) with MRC 3 or higher with dyspnea [104]. As a result, dyspnea VAS significantly decreased by 1.1 ± 0.33 cm compared to the baseline in the oral morphine group. In contrast, in the placebo group, the decrease was 0.35 ± 0.47 cm. However, there was no significant difference in the amount of change in the dyspnea VAS between the two groups. Constipation, nausea, and delirium were more common in the oral morphine group than in the placebo group.

As described above, previous reports have not yielded consistent results in terms of the effectiveness of opioids in relieving the symptoms of IPF patients with dyspnea, resulting in no high-quality evidence. However, many respiratory physicians have experienced in their clinical practice that dyspnea in IPF patients is extremely difficult to treat and significantly reduces patients' QOL. Therefore, opioids are also mentioned in the "Non-cancer Respiratory Disease Palliative Care Guidelines 2021″ as a treatment option for dyspnea that cannot be sufficiently relieved even with appropriate standard treatment [105]. Additionally, when using opioids, it is important to ensure that the prescribing physician is familiar with the method of use and adverse effects, that the standard treatment for the causes of dyspnea is being implemented, and that sufficient explanation and consent are given to the patient and patient's family; in addition, it is necessary to appropriately evaluate the effects and side effects following the start of opioids.

5.26. CQ24

Should lung transplantation be used for patients with IPF?

Advice based on expert consensus.

We advise patients with IPF who have no absolute contraindications to consider lung transplantation if these conditions are met.

5.26.1. Background

In Japan, the number of lung transplants for ILD (idiopathic and other ILD) includes 186 out of 350 brain-dead lung transplants, accounting for more than half; 71 out of 308 brain-dead bilateral lung transplants, accounting for one-fourth; and 90 out of 270 living-donor lung transplants, accounting for one-third (Japanese Lung and Heart-Lung Transplant Study Group, until December 2021). However, due to the current shortage of donors in Japan, the waiting period for brain-dead lung transplantation is long, approximately 2 years and 5 months, with IIPs being the disease with the highest mortality rate during the waiting period [106].

5.26.1.1. Explanation. In Japan, the prognosis of ILD patients registered for brain-dead lung transplantation during the waiting period is poor compared to other diseases, with reports indicating that 42–64% died during the waiting period [107–109]. In contrast, the median survival time after lung transplantation for IIP in Japan is 10.2 years [110], so it is expected that lung transplantation will prolong survival time. A report from a single overseas institution analyzed 46 IPF cases registered for lung transplantation and showed that patients who underwent lung transplantation had a reduced risk of death five years later [111]. Furthermore, some retrospective studies suggest that patients with pulmonary fibrosis who undergo lung transplantation have better long-term survival rates than those with other conditions, making them eligible for lung transplantation [112].

The benefits of lung transplantation include early determination of suitability and referral to a lung transplant facility, which is expected to increase survival rates, improve symptoms, and improve the post-transplant quality of life (physically and mentally) [113–115]. However, the harms include complications and mortality associated with surgery, the need to take immunosuppressive drugs for the rest of life, and the risk of graft rejection and infection. In severe respiratory diseases, where life expectancy is limited, the benefits may outweigh the harm.

Because there have been no prospective studies on the survival rate of lung transplant surgery for IPF patients or cost-effectiveness, considering the social activities gained through lung transplantation, we considered retrospective research data obtained from two studies on the Lung Allocation Score (LAS) [116,117], two studies on 6-min walking distance and waiting-list mortality rate [7,118], and three studies on waiting-list mortality rate [119–121]. It was shown that even in patients with IPF with high LAS, survival rates can be expected to improve with lung transplantation and that the prognosis for patients with ILD in Japan who are waiting for lung transplantation is poor.

Based on the above, after considering the retrieved objective data, we conclude that the determination of suitability for lung transplantation should be made as soon as possible once a diagnosis of IPF is made. It can take two–three months to confirm the diagnosis of a patient with suspected IPF, provide appropriate information, and provide support (on diagnosis, prognosis, and management), so it was believed that the first discussions on whether a patient with IPF is suitable for lung transplantation should begin at this time. Although it would take approximately 6 months to obtain a firm diagnosis to assess whether there were any absolute contraindications, lung transplantation should be discussed earlier, and referral to a transplant facility should be made if clinical necessity is demonstrated. Regarding the determination of suitability for lung transplantation, a consensus document was published by the International Society of Heart and Lung Transplants [122].

6. Conclusion

This revised 2nd edition was formulated in accordance with the "Minds Clinical Practice Guideline Development Manual 2020,'' a clinical practice guideline development manual by the EBM Promotion Project (Minds), Japan Council for Quality Health Care, commissioned by the Ministry of Health, Labor, and Welfare.

Clinical practice guidelines are a "document containing recommendations for optimizing patient care'' and "a type of decision-making material created to support patients and medical professionals.'' Although there are still many issues to be solved, we will continue to revise these guidelines so that we can do our best to care for IPF patients, and we will continue to strive to make them useful guidelines for clinical practice in Japan.

7. Future direction

In this section, we will clarify the improvements made in this second revised edition since the first edition, as well as the remaining issues for the future.

The characteristics of the evidence in this area are that there are only a small number of randomized controlled trials, and thus, it is necessary to use observational studies. Although it was decided to set seven new CQs during the revision process, two of them are important issues in clinical practice but ethically difficult to conduct randomized controlled trials, making it difficult to expect high-level evidence to continue going forward. However, we believe that it is necessary to provide a certain direction for the purpose of supporting the judgment of clinical practitioners, so we decided to present it as an expert consensus. Advice based on expert consensus is carefully designed and given to clinical practitioners by experienced experts, based on the characteristics of CQs and limited evidence. We will continue to examine whether this is the optimal presentation method for CQs based on important clinical issues.

Recommendations were determined through panel meetings, considering each of the GRADE criteria (balance of benefits and harms, certainty of the overall evidence, patient values and wishes, and utilization of medical resources). The criteria for determining indirectness in the GRADE system differed among panel members; therefore, the process of forming a consensus was as difficult as the last time. However, the final agreement was reached with the aim of ensuring that these guidelines are in line with the current clinical practice in Japan and that they ultimately benefit patients. In particular, regarding the use of medical resources, each facility has implemented many unique ideas for the benefit of patients, so it was a meaningful opportunity to compare each other's medical environments and gain new perspectives. We further discuss the process of making recommendations regarding the use of medical resources. Cost-effectiveness is an issue of rapidly increasing social interest. Discussions on how to handle such information in clinical practice guidelines, including cost, clinical usefulness, and safety, are rapidly intensifying, so it is necessary to closely monitor domestic and international trends to establish policies for the next revision.

It is recommended that clinical practice guideline formulation organizations appoint separate members to the panel responsible for conducting systematic reviews and determining recommendations. Due to personnel constraints, some committee members held both roles last time; however, this time, we were able to create an organizational structure that made them completely independent. That said, we were extremely concerned with sharing information. Due to the ongoing COVID-19 pandemic throughout the preparation of this revised second edition, committee members from each organization did not have the opportunity to meet in person and so held meetings online. For the systematic review team, four basic training sessions on systematic reviews and individual meetings were held online. We will continue to consider further revisions.

Finally, considering the current state of IPF treatment, the panel

consisted of respiratory specialists, with the exception of two methodology experts. In addition to these individuals, experts in respiratory surgery participated in this panel. However, because IPF is a highly specialized disease and team medical care is essential, we would like to consider the participation of a wide range of clinicians involved in the treatment of target diseases, including medical practitioners such as nurses, physical therapists, pharmacists who are involved in IPF care, and general practitioners who may come into contact with patients in primary care. Furthermore, the participation of patients, experts in medical policy and health economics, and those in the position of insurers who pay medical expenses in the future will also be an important issue for consideration. To reflect patients' values and wishes, we included the results of patient questionnaires to help understand patients' perspectives.

These guidelines did not sufficiently describe the examination and countermeasures, monitoring, and auditing of promoting and inhibiting factors when applying clinical practice guidelines. The awareness rate of these guidelines will continue to be an issue for the future. The awareness rate of IPF guidelines remains low; therefore, it is necessary to continue disseminating the guidelines. We hope that the second revised edition of the clinical practice guidelines will be disseminated to as many people as possible.

8. Revision schedule

These guidelines are scheduled to be revised every 4–5 years based on the results of new clinical trials. However, if important findings are obtained, we will consider bringing forward the revision date or making partial revisions, as necessary.

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Author contributions

Contributor Homma S was creation committee chairperson. Bando M, Date H and Suda T were the member of supervisory committee. Goto Y and Nakayama T were guideline creation expert. Kishi K, Azuma A, Kondoh Y, Johkoh T, Nishioka Y, Fukuoka J, Miyazaki Y and Yoshino I were the member of panel committee. Yamauchi H, Sakamoto S and Miyamoto A were guidelines secretariats. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

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