Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Review

Evaluation of clinical practice guidelines on treatment of cystic fibrosis: A systematic review

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ARTICLE INFO

Keywords:
Clinical practice guidelines
Cystic fibrosis
AGREE II
Pulmonary treatment

ABSTRACT

Background: Despite the existence of numerous clinical practice guidelines (CPGs) for cystic fibrosis (CF), there is limited understanding of their credibility and consistency. This systematic review aims to comprehensively evaluate the quality of CPGs for CF and its pulmonary complications, focusing on treatment recommendations for pulmonary care.

Methods: We conducted a comprehensive search across four databases and relevant websites to identify eligible guidelines providing treatment recommendations. The quality of these guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. Pulmonary treatment recommendations were analyzed and synthesized narratively.

Results: A total of 35 guidelines were identified. Most guidelines were of moderate quality according to the AGREE II instrument, with overall scores ranging from 21·05 to 76·13. Only six guidelines were recommended for use. These guidelines provide 359 pulmonary treatment recommendations for seven primary therapies and others. There was inconsistency in the use of airway clearance therapy, anti-inflammatories, antibiotics, inhaled drugs, and cystic fibrosis transmembrane conductance regulator modulator therapy. Four guidelines conditionally advocated for oral corticosteroids, while six opposed routine inhaled corticosteroids. One guideline discouraged lumacaftor–ivacaftor in the general CF population, two recommended only for children under 12 years old, and another strongly advocated for children between 2 and 5 years of age. However, one guideline noted a lack of evidence to recommend it for children under 6.

Abbreviation: ABPA, Allergic bronchopulmonary aspergillosis; ACBT, active cycle of breathing techniques; ACT, Airway clearance techniques; AD, Autogenic drainage; AGREE, Appraisal of Guidelines for Research and Evaluation; *B.cepacia*, *Burkholderia cepacia*; BAE, Bronchial artery embolization; CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; COI, Conflict of interest; CPGs, Clinical practice guidelines; FEV_1, Forced expiratory volume in one second; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICC, Intraclass correlation coefficient; IVA/LUM, Lumacaftor–ivacaftor; MRSA, Methicillin-resistant Staphylococcus aureus; NICE, National Institute for Health and Care Excellence; *P. aeruginosa*, *Pseudomonas aeruginosa*; PEP, Positive expiratory pressure.

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https://doi.org/10.1016/j.jcf.2025.02.005
Received 28 August 2024; Received in revised form 15 January 2025; Accepted 4 February 2025

Conclusion: The quality of CPGs for CF and its pulmonary complications has improved over time, reaching a moderate level generally, but there is still room for further improvement. Future efforts should focus on standardizing methodological frameworks and generating robust clinical evidence to enhance the overall quality and applicability of CF guidelines.

1. Introduction

Cystic fibrosis (CF), affecting over 89,000 individuals worldwide [1], is an autosomal recessive genetic disorder with multi-organ disease manifestation primarily attributed to the malfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein [1,2]. The respiratory system is most prominently affected in CF, resulting in a significant reduction in the quality of life and an increase in morbidity, mortality, and healthcare utilization. Despite advances in understanding and treating CF, the complexities of treatment remain substantial. In response to this multifaceted challenge, various medical societies and organizations worldwide have developed clinical practice guidelines (CPGs) with evidence-based recommendations for CF treatment [3–37]. However, inconsistencies in standards and methodologies have led to discrepancies among these guidelines [38].

Moreover, respiratory failure, often triggered by acute pulmonary exacerbation, remains a leading cause of morbidity and mortality in CF. The fundamental defect of CF results in impaired mucociliary clearance, mucus plugging and secondary infection, often involving bacterial pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*) [39]. With the increase in age of CF patients, chronic respiratory infections, marked by neutrophil-driven inflammation, are punctuated by acute exacerbations, causing loss of lung function and bronchiectasis [1]. As a result, meticulous daily management of lung disease, coupled with timely and aggressive treatment of exacerbations, is imperative in preserving lung function. The primary goal of CF therapy is to slow the progression of lung disease. However, there is limited knowledge about the level of agreement between existing CPGs for pulmonary management, which hinders clinical decision-making and underscores the need for a comprehensive evaluation of the available guidelines.

To bridge these disparities and address knowledge gaps, we employed the Appraisal of Guidelines for Research and Evaluation (AGREE) II [40], an internationally validated tool, to assess the methodological quality of guidelines and reflect their reliability. Remarkably, while prior review has focused on CF nutritional management guidelines to date [41], the quality of guidelines for the treatment of CF and CF pulmonary complications remains unclear. This uncertainty regarding the credibility of the guidelines poses challenges for clinical decision-making.

Therefore, our study aims to systematically evaluate the methodological quality of treatment guidelines for CF and CF pulmonary complications, specifically synthesizing and comparing the available recommendations for pulmonary treatment. Our efforts not only contribute to the ongoing development of guidelines but also provide clinicians with valuable insights into the quality and discrepancies within existing CPGs, ultimately enhancing the management provided to CF patients.

2. Methods

This study was preregistered in PROSPERO (CRD42022340220) and structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary file S1) [42].

2.1. Search strategy and selection criteria

A systematic search was conducted by two reviewers (WZ and XL) in conjunction with an experienced medical librarian through PubMed, Web of Science, Cochrane Library, as well as websites of relevant specialty societies, Guidelines International Network (GIN), and Google Scholar, from inception to March 12th, 2024. A complete search strategy is available in the Supplementary file S2.

We defined CPGs as documents that provided recommendations to guide practice, aiming to achieve the best possible individual health outcomes. CPGs that provided explicit treatment recommendations for CF and its pulmonary complications, published in English and Chinese were included. Inclusion and exclusion criteria are detailed in the Supplementary file S3.

2.2. Screening, data extraction, and synthesis of recommendations

The search results were screened by title and abstract, followed by full text by four independent reviewers (YH, JZ, MZ, and JL), and any discrepancies were resolved through consensus. Additionally, relevant supplementary files and methodological documents associated with each guideline were thoroughly examined. Data extraction was performed by two reviewers (JG and QL) and validated by a third reviewer (YH). A standardized form was used to extract data on the characteristics and bibliography of each guideline.

The treatment recommendations for lung were extracted and grouped into common therapies using narrative synthesis, which included both tabular and thematic analysis. Three appraisers (YH, MZ, and XK) independently evaluated the recommendations using a new comprehensive classification criterion (Supplementary file S4).

2.3. Quality assessment

Four reviewers (JZ, YZ, ZLZ, and ZYJZ) evaluated eligible guidelines using AGREE II, following comprehensive training and pre-grading to ensure consistency. Disagreements were resolved through consensus, especially those exceeding 3 points.

AGREE II includes 23 items across 6 domains: scope and purpose, stakeholder participation, rigor of development, clarity of expression, applicability, and editorial independence (Supplementary file S5) [43]. Each item was rated on a 7-point Likert score (1 = strongly disagree, 7 = strongly agree). Domain scores were a standardized score from 0 % to 100 %, with higher scores indicating higher quality. An overall score was assigned based on six domain scores, with double the weight given to the rigor of development and applicability [44]. Guideline was categorized as “recommended” (overall scores > 60 %), “recommended with modifications” (30 % - 60 %), or “not recommended” (< 30 %) [44].

2.4. Statistical analysis

Descriptive statistics were performed on the quality of eligible guidelines and the scope of pulmonary treatment recommendations. The AGREE scores were described by means and standard deviations, using an independent *t*-test or a Mann-Whitney test, and a one-way analysis of variance or a Kruskal-Wallis test as appropriate to compare. A linear regression was performed to examine the relationship between AGREE overall scores and the year of guideline publication. The agreement among all reviewers was measured by an intraclass correlation coefficient (ICC) with 95 % confidence intervals. All analyses were conducted using R software (version 4.2.2, R Foundation, Vienna, Austria).

3. Results

3.1. General characteristics

A total of 35 guidelines were identified (Fig. 1 and Supplementary file S6) [3–37]. The general characteristics of these eligible guidelines are presented in Fig. 2 and Supplementary file S7. The majority of the guidelines came from Europe and the United States (83 %), with 22 (63 %) being developed by the Cystic Fibrosis Foundation (CFF) and European Cystic Fibrosis Society (ECFS). Most guidelines are intended for the general CF population (80 %), with only four (11 %) specifically for infants or children and one (3 %) for pregnant women. Of these guidelines, thirty-two (91 %) guidelines were developed using evidence-based methods, but only 14 (40 %) graded the quality of evidence,12 (34 %) appraised the strength of recommendations, and five (14 %) employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for appraisal (Supplementary file S8). Notably, 12 (34 %) guidelines did not declare conflict of interest (COI) status and 26 (74 %) did not provide update plans.

3.2. Quality assessment

The agreement among the four appraisers was considered excellent (intraclass correlation coefficient, ICC: 0·86, 95 % CI: 0·82–0·89). The standardized AGREE II scores of the included guidelines are displayed in Table 1. The overall quality of the guidelines was moderate (Mean, 47·64; range, 21·05–76·13). Six (17 %) were categorized as "recommended" and 26 (74 %) were categorized as "recommended with modifications". Notably, there has been a significant improvement over time ($P < 0·001$), particularly after the publication of AGREE II instrument. Some domains showed considerable variation in scores (Fig. 3 and Supplementary file S9). The highest scoring domains were scope and purpose (Mean, 69·96; range, 33·33–100) and clarity of presentation (Mean, 79·44; range, 25·00–98·61). The score for stakeholder involvement (Mean, 55·63; range, 20·83–95·83) reached relatively acceptable levels. However, the rigor of development (Mean, 39·90; range, 5·21–84·38), editorial independence (Mean, 38·93; range, 0·00–100·00), and applicability (Mean, 28·66; range, 4·17–65·63) scored poorly.

Subgroup analysis by guideline characteristics is shown in Fig. 4. The quality of the guidelines published after 2009 has improved significantly ($P = 0·001$), with noticeable improvements in all areas except applicability. Evidence-based CPGs had higher scores, especially for those reporting evaluation systems for grading the quality of evidence or appraising the strength of recommendations ($P = 0·016$), which performed better in the rigor of development. Guidelines with updated plans also scored higher in rigor of development ($P = 0·031$). Additionally, guidelines reporting conflicts of interest tended to be of higher quality ($P < 0·001$). Further details are shown in the Supplementary file S10.

3.3. Pulmonary treatment recommendations

General recommendations for pulmonary treatment were extracted (Supplementary file S11). A total of 359 recommendations were identified from 28 guidelines, 43 (12 %) were strong recommendations, 90 (25 %) were weak recommendations, and the majority, 226 (63 %) were ungraded. Regarding the quality of evidence, 47 (13 %) were based on

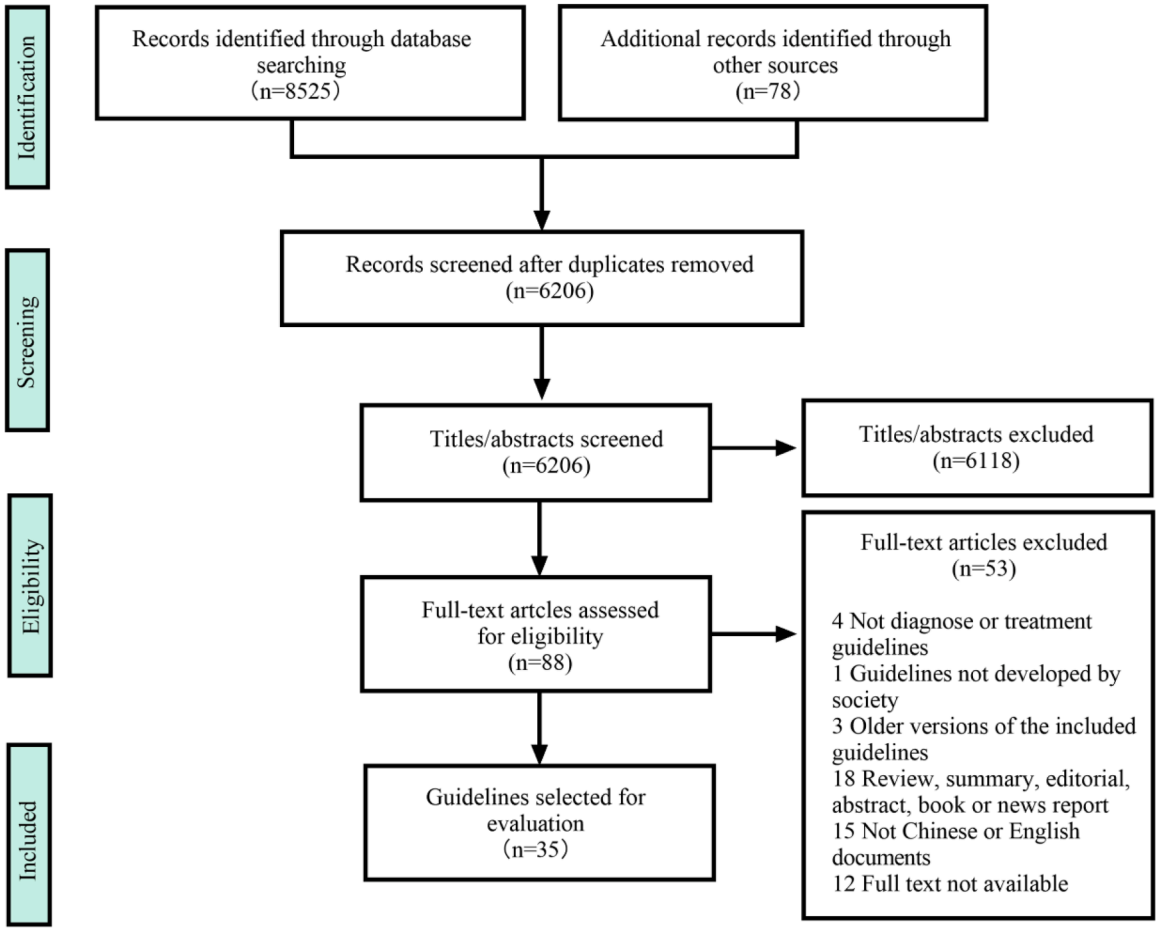

Fig. 1. Flowchart of guideline search and selection.

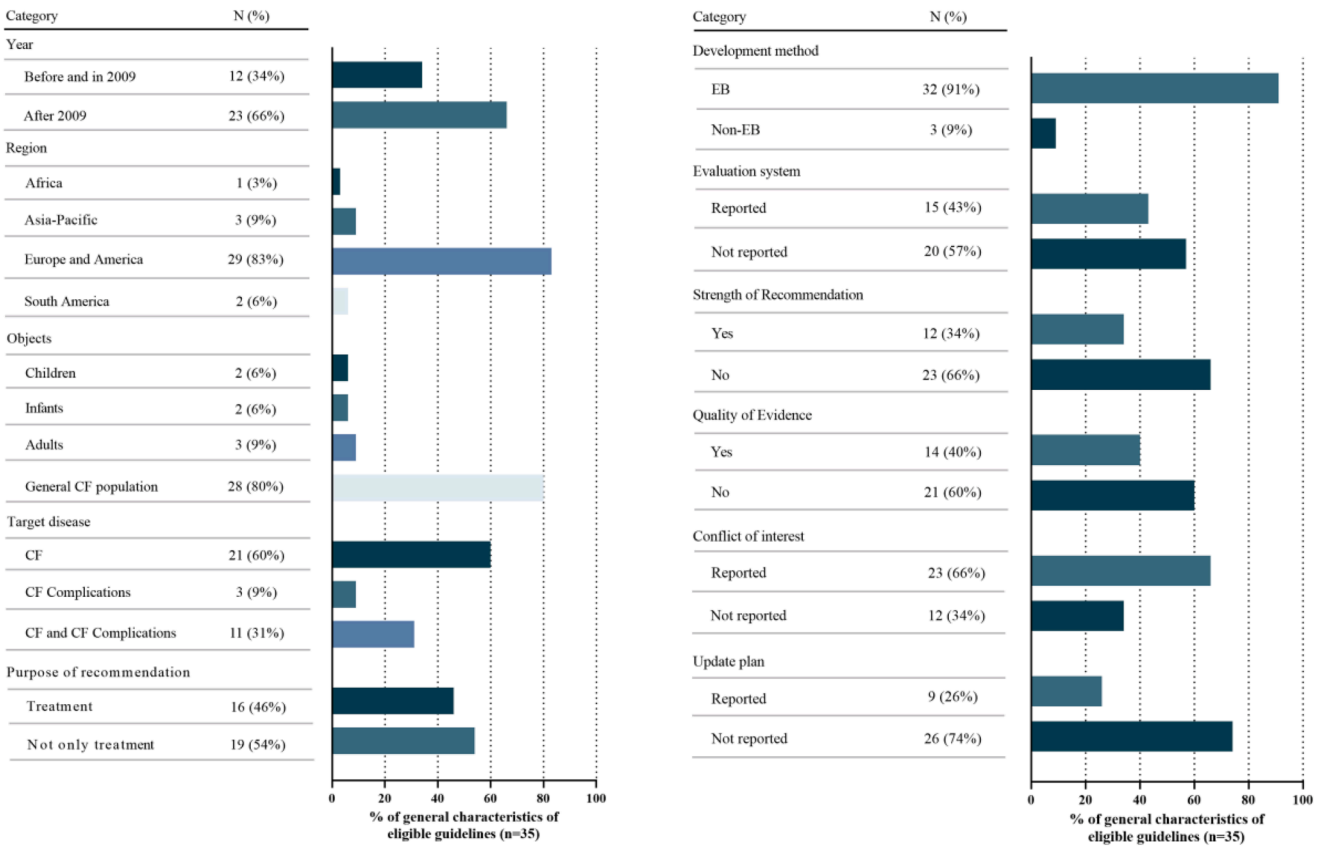

Fig. 2. The general characteristics of included guidelines. N (%) means the number and its proportion among 35 guidelines. *Abbreviations: CF, Cystic fibrosis;* EB, *Evidence-based.*

high-quality evidence, 66 (18 %) on moderate quality evidence and the majority, 246 (69 %) were low, very low or ungraded quality. These recommendations were categorized into seven major types of therapies and others, with some variations in detail. There was considerable variation in the recommendations for corticosteroids and lumacaftor–ivacaftor (IVA/LUM) (Supplementary file S12).

3.4. Airway clearance therapy

Thirteen (46 %, 13/28) guidelines provided 35 (10 %, 35/359) recommendations for airway clearance therapy (ACT), with one (3 %) being strong and three (9 %) based on high-quality evidence [4,11,12,14–16,20,23,24,27,29,34,35]. Multiple guidelines agreed that ACT should be used as part of treatment to improve lung function, regardless of age, [4,11,12,14,16,23,24] with two advocated individualized plans for CF patients with moderate quality evidence [11,29]. Autogenic drainage (AD) and active cycle of breathing techniques (ACBT) are effective forms of ACT [24]. For infants, the routine use of head-down drainage was not recommended [12,24]. Positive expiratory pressure (PEP) and oscillating PEP were also considered effective forms of ACT [24,27], but high-frequency chest wall oscillation was not recommended for routine use due to its low economic benefit [29]. However, no studies have demonstrated that any specific ACT is superior to others [11,27]. Additionally, two guidelines recommended expectorant drugs with high-quality evidence after 2017 [29,34], it should be noted that one of them supported the use of acetylcysteine [34], while the other did not [29]. A 2013 guideline indicated that the evidence was insufficient to recommend or oppose the long-term use of these drugs [20].

3.5. Anti-inflammatories

Eleven (39 %, 11/28) guidelines included 28 (8 %, 28/359) recommendations referred to the use of anti-inflammatories in CF patients, covering corticosteroids [7,12–15,20,23,27,29,32,34], ibuprofen [20,23,27], and leukotriene modifiers [7,20,23]. Eight (29 %) were strongly recommended and nine (32 %) were supported by high-quality evidence. The recommendations for inhaled and oral corticosteroids were heterogeneous. Four guidelines did not object to the use of oral corticosteroids in CF patients [20,23,27,29], but chronic use should be avoided [20,23,27]. Oral corticosteroids were considered for cases of persistent pulmonary exacerbations with high-quality evidence when azithromycin fails, while the duration of use was not specified [29]. Six guidelines recommended against the routine use of inhaled corticosteroids [12,13,20,23,27,34]. Two guidelines stated there is currently insufficient data to support the routine systemic use of corticosteroids in acute exacerbations or advanced cases [14,32]. For CF patients with allergic bronchopulmonary aspergillosis (ABPA), four guidelines consistently recommended the use of corticosteroids [7,20,23,34], although an early 2003 guideline stated insufficient evidence for inhaled corticosteroids [7]. Additionally, itraconazole was recommended if corticosteroid toxicity or recurrence of ABPA is present [7,34]. For ibuprofen, only one guideline recommended its chronic use in children aged 6–17 years under certain circumstances [20], and two guidelines noted a lack of evidence to either support or oppose its routine use in other age groups [20,23], while another advised against its use [27]. Three guidelines indicated insufficient data to form an opinion on leukotriene modifiers [7,20,23].

3.6. Antibiotics

Twenty (71 %,20/28) guidelines provided around one-third (36 %, 131/359) of recommendations regarding antibiotics for CF patients to treat bacterial infections [4–7,9,12–17,19–21,23,25,27,29,34,36], with 21 (16 %) strong recommendations and 18 (14 %) supported by

Table 1
The AGREE II domain scores of all included guidelines.

Guidelines	Overall Score (%)	AGREE II domain scores (%)					
		Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence
Daniel V. Schidlow (1993)[4]	28·82	55·56	36·11	9·38	84·72	16·67	2·08
J R Yankaskas (1998)[3]	21·05	33·33	23·61	15·10	25·00	19·79	16·67
G Döring (2000)[5]	29·90	65·28	23·61	17·19	68·06	15·63	16·67
A. Salcedo (2003)[6]	31·08	40·28	25·00	25·00	83·33	16·67	16·67
David A Stevens (2003)[7]	38·15	63·89	50·00	15·10	73·61	36·46	14·58
James R. Yankaskas (2004)[8]	45·44	75·00	45·83	25·52	75·00	34·38	47·92
Canadian Cystic Fibrosis Foundation (2006)[9]	42·45	59·72	41·67	27·08	86·11	42·71	12·50
F.P. Edenborough (2008)[10]	45·40	77·78	62·50	33·33	70·83	36·46	12·50
Flume PA (2009.4)[11]	49·00	68·06	69·44	73·44	72·22	10·42	14·58
Drucy Borowitz (2009)[12]	57·73	72·22	76·39	64·58	86·11	29·17	39·58
Harry Heijerman (2009)[13]	31·16	63·89	20·83	26·04	58·33	18·75	16·67
Flume PA (2009.11)[14]	32·51	63·89	37·50	28·65	72·22	4·17	20·83
Flume PA (2010)[15]	55·34	87·50	56·94	56·77	88·89	27·08	41·67
Isabelle Sermet-Gaudelus (2010)[16]	44·79	84·72	51·39	35·42	80·56	27·08	16·67
NICE Technology appraisal guidance (2012)[18]	46·70	45·83	58·33	41·67	77·78	37·50	33·33
NICE Technology appraisal guidance (2013)[19]	45·66	40·28	58·33	43·75	75·00	33·33	37·50
Mogayzel PJ Jr (2013)[20]	43·01	56·94	45·83	41·15	90·28	7·29	54·17
Mogayzel PJ Jr (2014)[21]	49·00	75·00	52·78	45·31	94·44	15·63	47·92
T O Hirche (2014)[22]	47·35	83·33	56·94	24·48	66·67	28·13	66·67
R Andres Floto (2016)[17]	56·55	100·00	69·44	63·02	98·61	20·83	16·67
Lahiri T (2016)[23]	66·88	81·94	88·89	72·40	90·28	43·75	41·67
Button BM (2016)[24]	61·72	69·44	56·94	67·71	69·44	53·13	56·25
NICE Technology appraisal guidance (2016)[26]	43·66	36·11	52·78	43·75	75·00	32·29	33·33
Athanazio RA (2017)[27]	52·86	80·56	36·11	40·63	91·67	34·38	64·58
Marco Zampoli (2017)[28]	35·33	86·11	41·67	5·21	86·11	29·17	0·00
NICE Guideline [NG78] (2017)[29]	76·13	84·72	86·11	84·38	81·94	65·63	56·25
Carlo Castellani (2018)[30]	45·18	59·72	58·33	33·85	86·11	26·04	37·50
Ren CL (2018)[31]	68·75	90·28	83·33	55·21	93·06	45·83	81·25
Kapnadak SG (2020)[32]	64·63	77·78	95·83	63·02	90·28	42·71	41·67
Katarzyna Walicka-Serzysko (2021)[33]	39·67	55·56	23·61	12·50	73·61	19·79	100·00
Pali Shah (2021)[25]	55·08	81·94	77·78	50·52	86·11	23·96	45·83
Chinese Medical Association (2022)[34]	40·97	95·83	43·06	9·38	68·06	17·71	66·67
Kevin W. Southern (2023)[35]	64·54	77·78	81·94	42·19	88·89	55·21	72·92
Athanazio RA (2023)[36]	54·77	80·56	72·22	63·54	83·33	10·42	54·17
China Alliance for Rare Disease (2023)[37]	55·95	77·78	86·11	40·10	88·89	25·00	64·58
Mean±SD	47·64±12·65	69·96±16·93	55·63±20·87	39·90±20·78	79·44±13·37	28·66 ±14·06	38·93±24·04
Range	21·05–76·13	33·33–100	20·83–95·83	5·21–84·38	25·00–98·61	4·17–65·63	0·00–100·00

Abbreviation: AGREE, Appraisal of Guidelines for Research and Evaluation.

high-quality evidence. *P. aeruginosa* infection is the most common target, with thirteen guidelines consistently recommending using antibiotics for treatment [5,9,12,13,16,19–21,23,27,29,34,36]. Combination antibiotics therapy was encouraged for patients with an exacerbation of pulmonary disease or resistant strain of *P. aeruginosa* [5,27,29], and aerosolized antibiotics can be used in combination with oral antibiotics [13,27,29]. Nine guidelines provided specific medications for *P. aeruginosa* infection [5,9,12,19–21,27,29,34]. Inhalation tobramycin was a well-accepted drug [5,9,12,19–21,27,29], and was suggested for chronic use [5,9,12,19,20,29]. Two guidelines recommended inhaled tobramycin as eradication therapy at 300 mg twice daily for 28 days with high-quality evidence [21,27]. Moreover, the long-term use of azithromycin was recommended for chronic *P. aeruginosa.* infection by three guidelines [11,27,34]. Colistin or colistimethate sodium was also considered effective [5,9,19,27,29] and was recommended as an alternative therapy [9,27], though one guideline stated there was insufficient evidence to recommend for or against the use of colistin as no obvious advantage [20]. Three guidelines opposed the use of prophylactic antipseudomonal antibiotics due to a lack of research support for their effectiveness [5,12,21].

Regarding other bacterial infections, two guidelines recommended treating nontuberculous mycobacterial infections with at least three antibiotics [17,27], usually including a macrolide. For *Burkholderia cepacia* (*B.cepacia*) complex strains infection, two guidelines recommended antibiogram-guided combination therapy for eradication [27,29], while one guideline stated a lack of evidence for or against this approach due to low-quality studies and the absence of regimen standardization [36]. One guideline provided information on methicillin-resistant *Staphylococcus aureus* (MRSA) eradication therapy using combinations of oral, topical, and inhaled drugs [27], such as sulfamethoxazole/trimethoprim, rifampin, fusidic acid, chlorhexidine, and vancomycin, while it was consistent with the other three guidelines in acknowledging insufficient data to recommend or not recommend this approach [12,23,36]. Additionally, two guidelines stated insufficient evidence to recommend for or against active attempts to eradicate *Staphylococcus aureus* in children under 5 years of age [12,23]. Three guidelines strongly recommended against prophylactic use of oral anti-staphylococcal antibiotics with moderate quality evidence [12,20,

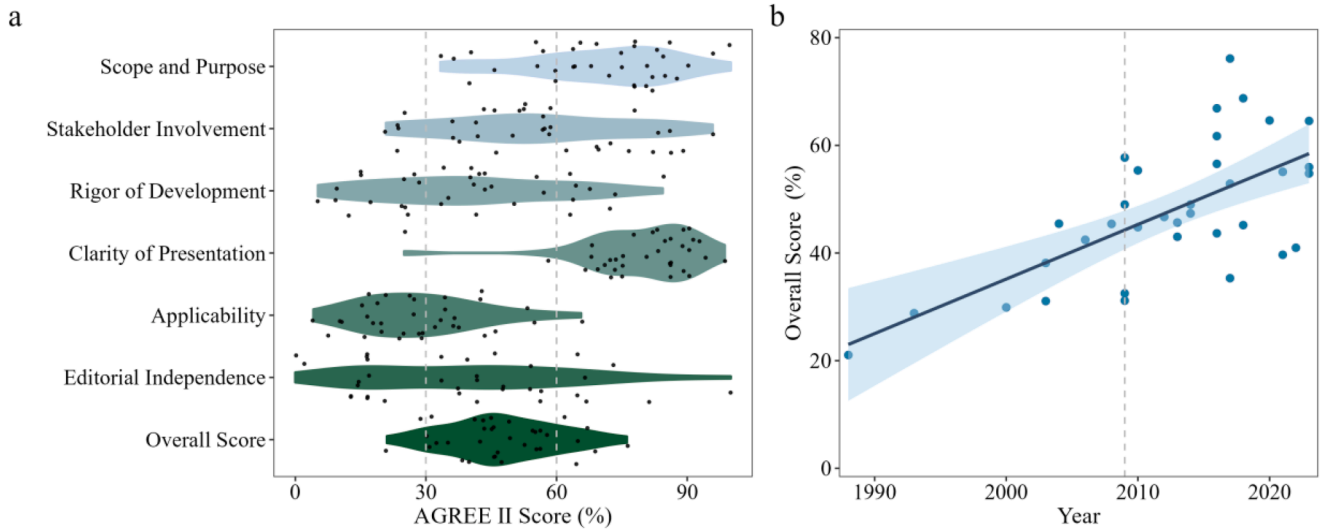

Fig. 3. AGREE II scores of all included guidelines. a. AGREE II domain scores and overall score of all included guidelines. A domain score higher than 60 % was considered as 'good', between 30 % and 60 % as "moderate" and lower than 30 % as "poor". b. The relationship between AGREE II overall scores and the published year of included guidelines. AGREE II was published in 2009. *Abbreviation: AGREE, Appraisal of Guidelines for Research and Evaluation II.*

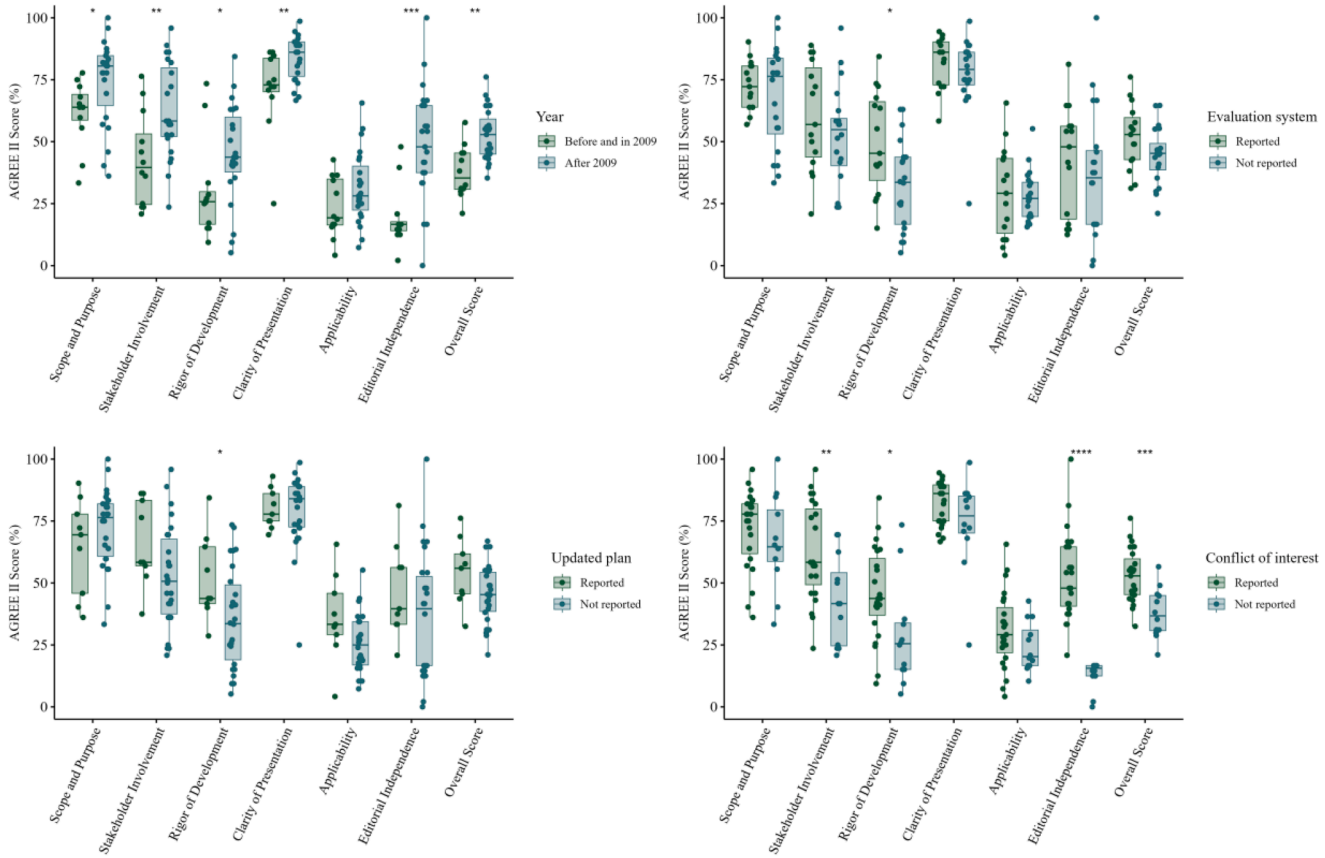

Fig. 4. Subgroup analysis of AGREE II scores in included guidelines by characteristics. *Abbreviation: AGREE, Appraisal of Guidelines for Research and Evaluation II.*

23], while one guideline recommended it may be indicated in infants, acknowledging a debate surrounding this issue [16]. But another suggested the prophylactic use of flucloxacillin in children under 6 years of age, rather than cefalexin [29]. Furthermore, azithromycin was recommended for long-term use in CF patients over 6 years of age with lung deterioration [20,29], but there was insufficient evidence to recommend for or against its chronic use in children aged 2 to 5 years [23].

3.7. Inhalation therapy

In addition to inhaled antibiotics, about half (54 %,15/28) of the guidelines recommended the use of other inhaled drugs for treatment [4,9,12,13,15,18,20,23–25,27,29,32,34,36], including dornase alfa [12,13,20,23,27,29,34,36], hypertonic saline [13,20,23,29,34], mannitol [18,27,29,34] and bronchodilators [9,13,20,23,27,34]. Of these 49 (14 %, 49/359) recommendations, nine (18 %) were strongly recommended

and thirteen (27 %) were supported by high-quality evidence. Multiple guidelines suggested using dornase alfa in CF patients [12,13,20,23,27,29,34,36], with two strongly recommending long-term use in patients 6 years of age and older [20,31]. Seven guidelines advised that CF patients should be treated with hypertonic saline [12,13,20,23,27,29,34], which can be used as a long-term treatment[13,20,34] with 7 % hypertonic saline being appropriate [12,27]. Mannitol dry powder was recommended to CF adults [18,27,29,34], commonly used when other inhaled treatments are unavailable or intolerable [18,29,34]. Four guidelines recommend the use of bronchodilators to treat bronchial hyperresponsiveness, bronchospasm, airway obstruction, persistent wheeze or asthma in CF patients [9,13,27,34], while two concluded that the evidence was insufficient to recommend for or against chronic use in CF patients [20,23].

3.8. CFTR modulator therapy

Nine (32 %, 9/28) guidelines, totaling 49 (14 %, 49/359) recommendations, guided CFTR modulators in CF patients [20,23,25–27,29,31,35,36]. Four (8 %) of these recommendations were strongly recommended and four (8 %) were supported by high evidence quality. Five guidelines suggested using ivacaftor for patients with specific gating mutations across different age groups [20,23,27,31,36], with high-quality evidence supporting its use in patients aged 6 years and older with at least one G551D CFTR mutation [20]. There were contradictory recommendations regarding the use of IVA/LUM in patients homozygous for the F508del mutation. Two guidelines advised against IVA/LUM for people aged 12 years and older [26,29], and one recommended it for children aged 2 to 5 years [35]. Additionally, one guideline discouraged the use of IVA/LUM in the general CF population [36], while another suggested there was no evidence to recommend it for children under 6 years [31]. However, one guideline acknowledged that IVA/LUM can reduce exacerbations and slightly improve FEV_1 in homozygous patients with high-quality evidence [27]. Guidelines published in 2023 already include tezacaftor-ivacaftor or elexacaftor-tezacaftor-ivacaftor as recommendations [35,36].

3.9. Oxygen therapy and ventilation

Five (18 %, 5/28) guidelines recommended oxygen therapy and ventilation in 15 (4 %, 15/359) recommendations [4,15,24,27,32], but most of the recommendations were ungraded in strength (73 %, 11/15) and quality of evidence (80 %, 12/15). Three guidelines recommended supplemental oxygen for CF patients with hypoxemia [4,27,32], while two highlighted the potential need for it during night or exercise [4,27]. Regarding ventilation, two guidelines suggested noninvasive ventilation as an adjuvant treatment for exacerbations like dyspnea [24,27], and two advised considering invasive mechanical ventilation in cases of respiratory failure [27,32].

3.10. Operative therapy

Eight (29 %, 8/28) guidelines included 34 (9 %, 34/359) recommendations for operative therapy in CF patients with hemoptysis, pneumothorax, and advanced pulmonary disease [3,4,15,17,25,27,32,34]. Most recommendations lacked graded strength of recommendation (97 %, 33/34) and quality of evidence (82 %, 28/34). Three guidelines suggested bronchial artery embolization (BAE) for patients with clinically unstable massive hemoptysis [4,15,27], and local pulmonary resection may be considered if BAE fails [4,15]. For patients with recurrent pneumothorax, two guidelines recommended undergoing pleurodesis to prevent recurrence [15,27]. In four guidelines [3,27,32,34], lung transplantation was considered as a final treatment option for individuals with advanced and severe pulmonary disease, with two providing specific indications [27,34].

3.11. Others

Eight (29 %, 8/28) guidelines covered 18 (5 %, 18/359) recommendations related to additional therapies, most being ungraded in recommendation strength (94 %,17/18) and quality of evidence (94 %,17/18) [4,12,14–17,25,32]. These recommendations included hemostatic measures for hemoptysis [4], chest tubes use for pneumothorax [15], antibody prevention of viral infection [12,16], as well as strategies for managing acute pulmonary exacerbations [15], pulmonary hypertension and pulmonary refractory respiratory failure [32], and immunotherapy [17,25].

4. Discussion

To our knowledge, this is the first study to critically appraise treatment CPGs for cystic fibrosis and its pulmonary complications, with a particular focus on summarizing the recommendations related to pulmonary symptoms in CF. The quality of these guidelines has improved over time, reaching a moderate level. However, significant inconsistencies and heterogeneity in pulmonary recommendations across the identified guidelines highlight ongoing uncertainty in CF management and the lack of extensive research in this area. This suggests that although progress has been made, further improvement is needed to ensure broader access to high-quality guidelines.

The improvements observed in CF CPGs can largely be attributed to the introduction and widespread use of standardized evaluation tools and methods, such as AGREE II and GRADE [45,46], which provided a structured framework for guideline development. Since the publication of AGREE II, the most significant enhancement has been observed in editorial independence, with the average score rising from 19·27 to 49·18. This positive shift is likely due to the relative simplicity of this domain, which primarily involves reporting external funding and conflicts of interest, as well as detailing how these potential biases are managed. Furthermore, the involvement of multidisciplinary personnel in the guideline development process has contributed to improved stakeholder involvement domain, further enhancing the overall quality of the guidelines. Advancements in clinical research methodologies and the growing body of evidence have also significantly strengthened the evidence base for CF guidelines. Although some evidence quality remains suboptimal or less robust, it has nonetheless laid the groundwork for a more rigorous development process. Domains such as scope and purpose and clarity of presentation, which were already well-executed, have achieved even better scores. However, applicability remains unsatisfactory and continues to be one of the most significant challenges facing CF guidelines, despite slight improvement.

Despite the progress made, the improvements in the quality of CF guidelines remain insufficient, particularly in the domain of applicability with the lowest scores. This indicates that more focused efforts are needed to ensure that the recommendations are not only based on high-quality evidence but are also feasible and relevant to real-world clinical settings. One critical issue that needs to be addressed is editorial independence, which plays a pivotal role in ensuring that the recommendations are unbiased and not influenced by external factors such as pharmaceutical companies [47]. COI represent a significant source of bias in guideline development [48], and it is concerning that approximately one-third of the evaluated guidelines failed to report them at all. A more proactive approach to gathering COI information and mandating that individuals with COI recuse themselves, either fully or partially, from the guideline development group could help ensure editorial independence and minimize external influences on the recommendations [49].

Moreover, it was noted that many guidelines lacked a clear link between their recommendations and the supporting evidence, and the procedures for formulating recommendations were often insufficiently detailed. This undoubtedly leads to ambiguity and undermines clinicians' confidence in the guidelines. It is imperative to provide a clearer

explanation of the evidence base and employ rigorous and standardized methods to avoid any potential confusion [50]. Additionally, external review and update procedures are essential for ensuring transparency and credibility of the guidelines over time [51,52].

To enhance the inclusivity and applicability of guidelines, it is vital to engage a diverse range of stakeholders in the development process, including patients, healthcare providers, health economists and policymakers. This approach not only reflects a broad spectrum of expertise and perspectives but also directly improves the applicability to patient care. However, applicability remains the most challenging area, as many CF guidelines have not sufficiently addressed the facilitators (e.g., educational strategies) and barriers (e.g., patient compliance, economic constraints or sociopolitical contexts) associated with the application of their recommendations. This issue is common across contemporary CPGs and must be addressed to improve the likelihood of guideline uptake in clinical practice [53,54]. Recommendations are only effective when actively adopted in real-world clinical settings, and therefore, it is essential that guidelines account for the complexities of real-world implementation.

Incorporating implementation science into the planning, development, and execution of guidelines can help facilitate their successful uptake and make a substantial impact on clinical practice [55]. Pilot testing guidelines in clinical settings prior to the publication may also prove valuable [56,57], as it allows for the identification of potential issues and barriers to implementation. By testing the feasibility and effectiveness of recommendations in specific settings, we can uncover challenges that might not be apparent during the initial development process [53]. Furthermore, guidelines should ensure that the research underlying their recommendations is relevant to the target population, as clinical outcomes can vary depending on factors such as ethnicity, age, and underlying health conditions. Integrating research that reflects the characteristics of the population for which the guidelines are intended can enhance their feasibility and applicability in diverse clinical contexts [58].

The impact of CF on the lungs is the most easily perceived and reflected. Therefore, it is highly beneficial to extract and evaluate clinical recommendations on pulmonary treatment to provide considerable guidance for clinicians. ACT is an important aspect of symptomatic management, and the universal applicability of ACT to CF patients of all ages is widely recognized. However, it cannot be overlooked to personalize programs based on individual patient differences such as age, patient preference, and adverse events [11,29]. Conventional chest physiotherapy, including clapping, percussion, vibration, and postural drainage, has relatively modest effectiveness, with unproven long-term benefits [59]. For infants, particular attention should be paid to the implementation details of postural drainage [12,24], as inappropriate positions can lead to reflux and aspiration [60]. Currently, there are various ACTs for CF patients, including ACBT, AD, and high-frequency chest compression [24,59], but none of these methods is superior to the others [61,62]. Poor patient compliance is a challenge in the implementation of ACT [63,64], which underscores the importance of incorporating patients' preferences and views into the development of guidelines to assist the personalized prescriptions. PEP is also recognized as an effective form of ACT that significantly reduces pulmonary deterioration [65], further enriching the implementation methods of airway clearance and providing more options for clinical practice. Additionally, expectorant drugs, which can alter mucus activity to help discharge airway secretions, were recommended in the guidelines published in or after 2017 [29,34]. While the recommendations regarding acetylcysteine exhibit heterogeneity, likely due to the dynamic nature of the evidence, inconsistent standards for evidence evaluation, and differing perspectives on clinical applicability. What's more, clinicians should remain vigilant regarding the appropriateness of ACT for patients experiencing pneumothorax and hemoptysis [15].

The use of corticosteroids in CF patients remains controversial, and guidelines differ on how and for how long corticosteroids should be used. Some guidelines opposed the use of inhaled corticosteroids in CF patients [12,13,20,23,27,34], while others supported the oral administration of corticosteroids but do not recommend long-term use due to substantial side effects [20,23,27]. A systematic review concluded that the routine use of inhaled corticosteroids in CF patients is not significantly better than placebo or non-steroid medication in improving lung function [66]. Some studies have even suggested that it may affect growth and lung function in children [67,68]. Chronic use of oral corticosteroids can also increase the risk of edema, obesity, osteoporosis, hypertension, and diabetes [69]. However, corticosteroids can be used in CF patients with asthma or ABPA since they are effective in reducing bronchial hyperreactivity [70], but the benefits must be weighed against potential harms. In specific cases, ibuprofen was considered to slow the loss of lung function in patients aged 6–17 years [20,71], with high doses potentially being more effective [71,72]. However, due to the high incidence of adverse events like gastrointestinal bleeding and the difficulty in monitoring serum drug levels [27,72], it cannot be used routinely and is not recommended for other age groups. The use of leukotriene modulators has not been adequately demonstrated in clinical studies to be beneficial [7,20,23]. In short, anti-inflammatory drugs need to be used carefully depending on the patient's condition, with close monitoring of efficacy and side effects. When formulating guideline recommendations, it is essential to leverage existing evidence to balance the relationship between benefits and risks.

CF patients are highly susceptible to respiratory tract bacterial infections and require regular intensive antibiotic treatments. The use of antibiotics in *P. aeruginosa* infection is generally accepted. Tobramycin is the most commonly recommended drug, followed by azithromycin and colistin. Tobramycin, an aminoglycoside antibacterial with good activity, is delivered via inhalation to improve lung function and reduce sputum *P. aeruginosa* density, thus minimizing ototoxicity and nephrotoxicity associated with intravenous delivery [73]. Azithromycin not only modulates inflammatory pathways but also has extensive effects on the immune system [74]. It has also gained acceptance as a potential anti-inflammatory therapy for lung disease [75]. Long-term use was recommended for CF patients over 6 years of age [20,29]. Antibiotic combination therapy is employed in cases of worsening lung disease and the emergence of drug-resistant bacteria [5,27], as it may delay antibiotic resistance and create potential synergies [5]. Non-tuberculous mycobacterium infection was recommended to be treated with a combination of no fewer than three antibiotics, usually including macrolides [17,27]. For *B.cepacia* complex strains and *Staphylococcus aureus*, there was no high-quality evidence to support eradication therapy. Additionally, guidelines consistently did not recommend the use of prophylactic antibiotics to prevent the acquisition of *P. aeruginosa* and *staphylococcus*, but oral anti-staphylococcal antibiotics may be beneficial for infants [76,77]. The prolonged use of antibiotics is usually accompanied by drug resistance, and guidelines should provide more auditing standards regarding the dosage, frequency, and duration of drug use to improve clinical application. There was relative agreement on the overall view of other inhaled drugs, such as dornase alfa, hypertonic saline, mannitol dry powder, and bronchodilators. However, attention should be given to voice alteration and rash associated with the use of dornase alfa [78]. The choice of medication should be based on individual patient conditions. Adults can use mannitol dry powder when other inhaled treatments are unavailable or intolerable [79]. Additionally, bronchodilators can be used in the presence of asthma or bronchospasm.

CFTR modulator therapy, as an emerging treatment, has brought great hope to CF patients and holds tremendous potential. Guidelines consistently supported the use of ivacaftor for patients with specific gating mutations. The age of use of IVA/LUM was heterogeneous, and the NICE technology appraisal guidance opposed its use in people over 12 years of age [26], consistent with the standard for CFTR variant-specific treatment with recommendations in preschoolers [35]. However, a Brazil guideline opposed its use in the general CF population

due to the low quality of available clinical trial evidence [27]. Although IVA/LUM is associated with an increase in early transient shortness of breath and a long-term increase in blood pressure in adults, it significantly improves respiratory function in children under 12 years of age without apparent immediate safety concerns [80]. Therefore, caution is advised in the clinical application of this dual therapy, as there are still many potentially adverse effects to be reported [36]. The 2023 guidelines also recommended another dual (tezacaftor-ivacaftor) and triple (elexacaftor-tezacaftor-ivacaftor) therapy due to their superior safety profiles [35,36]. However, further high-quality clinical evidence is needed to support this, it is necessary to accelerate clinical trials of this new approach to establish optimal applications. In addition, cost is also a factor to consider [81], as it is a major barrier to CF patients benefiting from this therapy. Regrettably, few current guidelines mentioned cost-effectiveness, and this was evident across other treatments as well.

In terms of ventilation improvement, some guidelines provided effective support to improve respiratory function and overall prognosis. Supplement oxygen was recommended to correct hypoxia in daily life [4,27,32], and timely mechanical ventilation was advised in case of acute aggravating symptoms such as breathing distress or failure. In the presence of urgent and severe pulmonary conditions, guidelines unanimously agreed on the scope of operative therapies, including pleurodesis to prevent pneumothorax recurrence [15,27], bronchial artery embolization and local pulmonary resection for treating hemoptysis [4,15,27], and lung transplantation as a last resort for advanced pulmonary disease [3,27,32,34]. Respiratory and circulatory function, survival probability, expected quality of life, and patient compliance should be fully evaluated before lung transplantation [27,34,82]. Additionally, it is necessary to prevent postoperative immune rejection [83]. For such operational treatment, providing additional materials with innovative methods, such as infographics, e-Health technologies, online educational videos, and "living" documents, can significantly increase users' awareness and acceptability of guideline recommendations, further facilitating clinical implementation. Beyond the seven primary therapies, there was also a small subset of recommendations concerning CF comorbidities and advanced lung diseases, characterized by their diversity. Given the rarity and complexity of CF, most of these recommendations were based on expert opinion. Nevertheless, these recommendations, as an indispensable part of CF treatment progress, are crucial for providing guidance despite gaps in evidence.

In this review, we observed that many recommendations lacked sufficient or high-quality evidence, which may be a contributing factor to the limited improvement in the domain of rigor of development. For instance, most recommendations for infants and children were extrapolated from adult evidence, leading to weak strength. However, the absence of high-quality evidence does not necessarily equate to poor-quality guidelines [84]. It is widely acknowledged that high-quality clinical evidence may be limited or unavailable for special populations (e.g., children, pregnant women, elderly patients), comorbidities, or public health emergencies [85,86]. In such conditions, low-quality evidence may still represent the best available practice at that time, providing valuable guidance for clinical decision-making in the absence of robust clinical data [84]. Similarly, recommendations based on expert consensus do not undermine the value of the guidelines or impede their adoption in clinical practice, instead, they reflect the current state of knowledge in the field [87]. A transparent and scientifically rigorous development process is crucial for formulating recommendations, ensuring that they—whether based on high-quality clinical trials or expert consensus—are clearly articulated and explicitly demonstrate their strengths and limitations. Meanwhile, thorough documentation of the development process allows clinicians to understand the rationale behind the recommendations and apply them appropriately. As research advances and more effective treatments for CF patients are introduced, the development of specialized guidelines tailored to specific populations becomes an inevitable requirement in clinical development. This highlights the importance of designing well-structured clinical trials and accelerating research progress, which in turn, enhances the quality of CF guidelines. In addition, the evolving clinical evidence [88], along with inconsistent methods and standards for evidence development, are the primary causes of recommendation heterogeneity. Addressing these discrepancies requires timely guideline updates and establishment of standardized methodological frameworks [89]. In this context, the AGREE II framework and a more systematic approach are strongly recommended to ensure high-quality guideline development.

This study comprehensively searched multiple databases and society's websites to identify relevant guidelines. However, a potential limitation is the inclusion of only freely available guidelines and the selection of those published in English or Chinese, which may result in the omission of some relevant guidelines, thereby affecting the comprehensiveness of the study. Moreover, while the AGREE II tool was used to assess the methodological quality of the guidelines, it should be noted that the quality of guidelines evaluated by this tool does not guarantee the true effectiveness and applicability of the recommendations in clinical practice. Furthermore, this study only focused on pulmonary treatment recommendations within the guidelines. Future research should aim to evaluate all the recommendations to facilitate the development and refinement of comprehensive guidelines.

5. Conclusion

This review highlights the key issues that need attention when developing guidelines for cystic fibrosis and reveals inconsistencies in pulmonary treatment recommendations. Standardizing methodological frameworks and accelerating the pace of well-designed and high-quality clinical trials, especially for vulnerable populations, are crucial. These efforts will enhance the reliability and quality of guidelines, enabling developers to effectively update existing guidelines and develop standardized guidelines. Consequently, clinicians will be more inclined to utilize these recommendations in clinical practice.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed in this study are included in the supplementary file.

Declaration of competing interest

The authors declare that they have no competing interests.

Funding

This study was funded by Guangzhou Medical University 2022 Student Innovation Ability Improvement Program, the National Natural Science Foundation of China [82370056] & Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences [2023-I2M-C&T-A-002], Natural Science Foundation of Guangdong Province (2023A1515010308), the Project of 2022 Student Innovation Ability Enhancement Program of Guangzhou Medical University (02-408-2203-2106), Guangdong Province 2022 Graduate Education Innovation Plan project (2022ANLK049).

Authors' contributions

JM and XT were responsible for the study concepts and design. JM

and YH designed the methods. JG, QL, WZ, and XL contributed to the literature review and data extraction. YH, JZ, MZ, XK, YZ, ZLZ, JL, and ZYJZ accessed and managed data. YH and JZ performed the statistical analyses and interpretation. JM and YH prepared the first draft of the manuscript, with important contributions from MZ, ZW and JL. All authors interpreted the results, commented on drafts of the manuscript, and approved the final version. All authors had full access to all the data in the study and decided to submit it for publication.

Acknowledgements

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.02.005.

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