Disease Severity and Activity in Bronchiectasis

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Disease Severity and Activity in Bronchiectasis: A Paradigm Shift in Bronchiectasis Management

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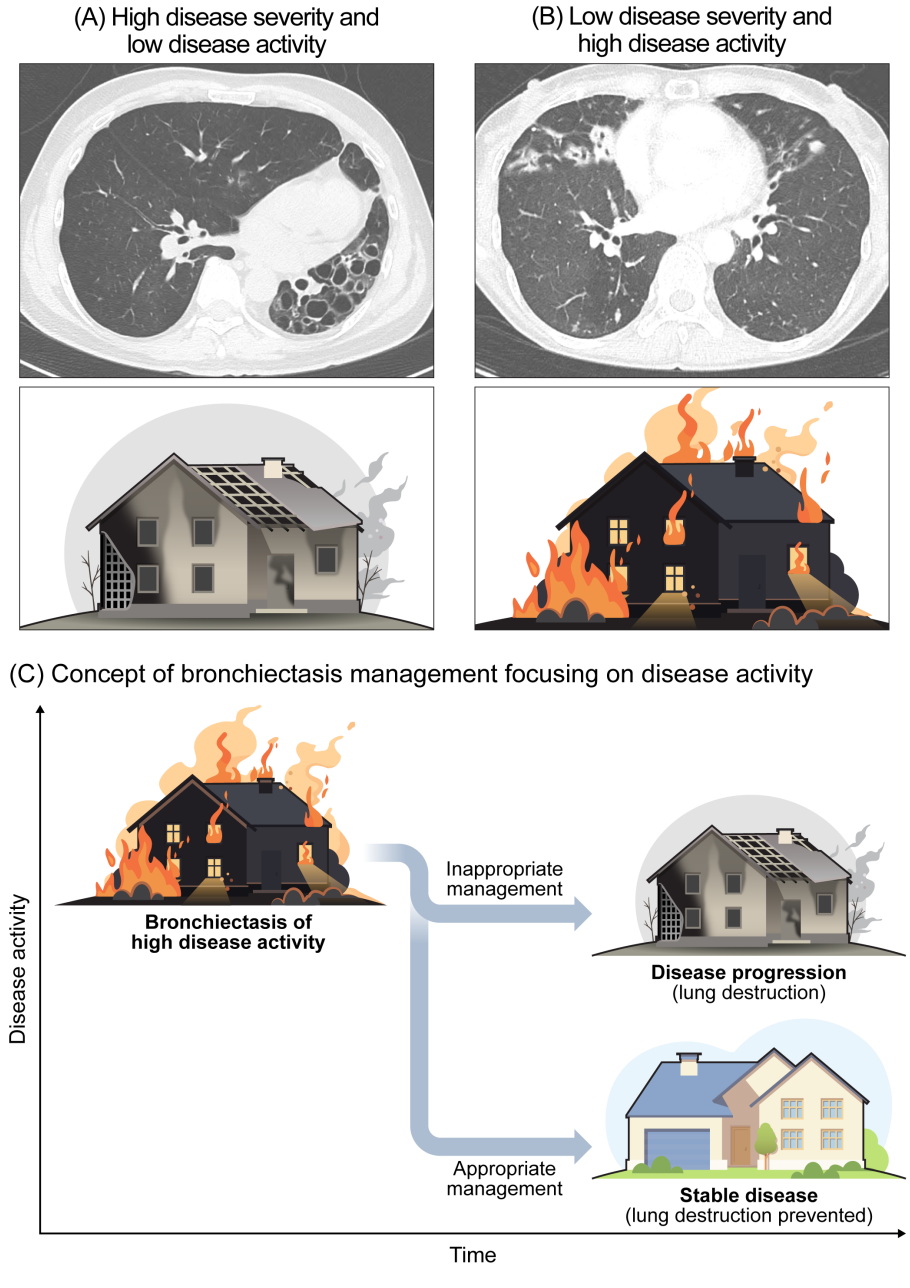


Abstract

Bronchiectasis has an increasing prevalence and substantial clinical and economic burden. Therefore, physicians should identify patients with bronchiectasis at high risk of disease progression to ensure optimal management in advance. The heterogeneity of bronchiectasis means it is unlikely that any single parameter could identify high-risk patients; therefore, disease severity is usually assessed using validated composite tools, such as the Bronchiectasis Severity Index, FACED, and Bronchiectasis Aetiology Comorbidity Index, to predict long-term outcomes in bronchiectasis. Disease severity, however, implies an advanced process with lung destruction. Earlier intervention may prevent disease progression and improve outcomes. To identify patients at risk, rather than patients with established advanced disease, we need to shift our focus from disease severity to disease activity. Disease activity denotes the activation level of underlying pathophysiological processes and can be measured using clinical presentations and biomarkers. This review discusses a paradigm shift in bronchiectasis management, focusing on disease activity rather than severity, to prevent disease progression.

Keywords: Bronchiectasis; Severity of Illness Index; Inflammation; Disease Progression

Introduction

Bronchiectasis is defined radiographically as permanent dilatation of the bronchi and clinically as persistent productive cough and recurrent chest infections[1-3]. Although bronchiectasis was considered a rare disease in the past, its prevalence and incidence are increasing globally and are consequently associated with substantial clinical and economic burden[4-11]. These epidemiological reports have caused renewed interest in the disease and an increase in clinical research, which has provided more evidence-based treatment options, including novel drugs under development[12].

Although more treatments for bronchiectasis are becoming available, physicians need to identify patients at high risk of disease progression to ensure optimal management in advance. The key to bronchiectasis management is to treat patients with high disease activity in a timely manner to prevent disease progression and poor long-term outcomes. However, bronchiectasis is a heterogeneous disease because it is the final common pathway for various infectious, genetic, autoimmune, developmental, and allergic diseases[13]. This heterogeneity limits the determination of a single clinical parameter or biological marker to identify patients with bronchiectasis at high risk for poor long-term outcomes. In this review, we discuss the definitions of disease severity and activity in bronchiectasis, validated tools for assessing disease severity, and the clinical and biological markers for measuring disease activity.

Definitions of Disease Severity and Activity

Disease severity refers to the extent of organ system dysfunction or physiological decline experienced by an individual. It provides a measure for understanding the effects of disease on resource utilization and long-term clinical outcomes[14]. Disease severity, usually assessed using risk stratification tools, helps clinicians identify patients at high risk of future mortality, exacerbations, and hospital admissions. Typically, disease severity is categorized as mild, moderate, or severe based on these criteria.

Disease activity is a biological term, in contrast to disease severity. Disease activity pertains to the biological aspects, focusing on the level of activation of the underlying pathological processes driving the disease[15]. Ideally, disease activity can be identified and measured using validated biomarkers that provide insights into the active state of the condition[15]. Disease activity varies owing to changes in exposure to eliciting triggers and in response to treatment[16]. Therefore, disease activity, which is usually assessed using biomarkers, is valuable for identifying patients who are more prone to disease progression and for predicting responses to certain types of treatment.

In simple terms, we may consider disease severity in bronchiectasis a measure of the amount of lung damage that has occurred, while disease activity refers to the rate at which further lung damage is occurring.

Disease Severity in Bronchiectasis

1. Bronchiectasis Severity Index

The Bronchiectasis Severity Index (BSI), the first severity assessment tool for patients with bronchiectasis, was developed in 2014[17]. This was derived in a United Kingdom cohort (n=608) and validated in four European cohorts (n=702); the end points of the study were mortality, hospitalization for severe exacerbations, exacerbations, and quality of life. Cox proportional hazards regression analysis identified nine variables (older age, lower body mass index [BMI], prior hospitalization, frequent exacerbations in the year before the study, dyspnea, lung function, *Pseudomonas aeruginosa* colonization, colonization with other pathogenic organisms, and three or more lobes involved in high-resolution computed tomography [CT]) or cystic dilatation that were independently associated with both mortality and hospitalization among patients with bronchiectasis. Points are awarded based on the strength of association with outcomes to create a total score. An online calculator is also provided at http://www.bronchiectasisseverity.com to aid in calculating the score. The BSI score ranges from 0 to 24 and classifies patients into three groups: mild (0–4 points), moderate (5–8 points), or severe (≥9 points). Distinct differences in mortality and hospitalization outcomes were observed among the three severity groups (Table 1).

However, patients with active malignancy or nontuberculous mycobacterial (NTM) pulmonary disease were excluded from the study. Therefore, the validity of this tool in patients with bronchiectasis attributable to active cancer or NTM pulmonary disease remains undetermined[17]. Furthermore, the BSI tool was derived and validated in European patients with bronchiectasis, and it may show different performance in Asian patients. A Chinese study evaluated the performance of BSI in patients with post-tuberculosis (TB) bronchiectasis, a major etiology of Asian bronchiectasis[18]. Although the BSI demonstrated efficacy in predicting mortality in post-TB bronchiectasis, it showed limitations in predicting admission and exacerbation. Additionally, a recent Indian study revealed that infection with Enterobacterales, particularly *Klebsiella pneumoniae*, was associated with increased mortality, whereas *P. aeruginosa* was associated with exacerbations but not with mortality[19]. Given the different microbiology and etiology profiles in Asia compared with those in Europe[19-21], the applicability of the BSI in this population warrants future studies.

2. FACED and exacerbation added to FACED scores

The FACED score was developed using a Spanish bronchiectasis cohort (n=819), and 5-year all-cause mortality was the endpoint[22]. Of the study population, 397 patients were randomly selected for score construction, and the remaining 422 were used for validation. Logistic regression analysis identified five dichotomized variables, including forced expiratory volume in 1 second (FEV_1) (F) classified as either ≥50% or <50%; age (A), categorized as <70 or ≥70 years; presence of *P. aeruginosa* colonization (C); radiological extension (E), scored based on the affected numbers of lobes; and dyspnea (D), assessed using the modified Medical Research Council (mMRC) scale, which collectively form

Table 1. Bronchiectasis Severity Index

Severity marker	Points						
	0	1	2	3	4	5	6
Age, yr	<50		50–69		70–79		≥80
BMI, kg/m^2	≥18.5		<18.5				
FEV_1% predicted	>80	50–80	30–49	<30			
Hospital admission before the study	No					Yes	
Exacerbations before the study	0–2			≥3			
MRC dyspnea score	1–3		4	5			
Pseudomonas colonization	No			Yes			
Colonization with other organisms	No	Yes					
Radiological severity: ≥3 lobes involved or cystic bronchiectasis	No		Yes				

Bronchiectasis Severity Index risk: 0–4 points, mild; 5–8 points, moderate; >8 points, severe.
BMI: body mass index; FEV_1: forced expiratory volume in 1 second; MRC: Medical Research Council.

the FACED score. The FACED score ranges from 0 to 7 and classifies patients into three groups: mild (0–2 points), moderate (3–4 points), or severe (5–7 points). Distinct differences in mortality outcomes were observed among the three severity groups.

However, a fundamental limitation of the FACED score is that it was developed to predict mortality in patients with bronchiectasis and not to predict other outcomes, such as hospitalizations and exacerbations. Therefore, the same study group subsequently developed the exacerbation added to FACED (E-FACED) score incorporating several exacerbations, which was designed to predict future exacerbations[23]. The E-FACED score added the variable of at least one severe exacerbation in the previous year (E), either yes or no, to the five FACED score variables. The E-FACED score ranges from 0 to 9 and classifies patients into three groups: mild (0–3 points), moderate (4–6 points), or severe (7–9 points) (Table 2). Although the FACED and E-FACED scores have also been validated in patients from Latin America[23,24], they may perform differently in Asian patients. In the aforementioned Chinese study, E-FACED showed limited efficacy in predicting admission and exacerbation of post-TB bronchiectasis[18]. Further studies are warranted to determine its usefulness in Asian populations. An important limitation of FACED is the lack of exacerbations as a predictive variable, while the inclusion of severe exacerbations only in the E-FACED score limits its generalizability because the criteria for hospitalization are so different across different healthcare systems.

3. Comparison between BSI and E-FACED

Both the BSI and E-FACED scores seem to be valuable for predicting long-term outcomes in bronchiectasis. Both indices assign points based on age, lung function, chronic *P. aeruginosa* infection, radiological extent, severe exacerbation, and degree of dyspnea. Furthermore, the BSI incorporates other variables, such as BMI, exacerbation frequency, and chronic colonization with bacteria other than *P. aeruginosa*. Both scores categorize patients into low-, moderate-, and high-risk groups using varying thresholds.

A few studies have directly compared the predictive performance of the BSI and FACED. A single-center retrospective study included 91 patients with bronchiectasis, with a median of 18.8 years of follow-up. Notably, both scores had similar predictive power for 5-year mortality (area under the receiver operator characteristic curve [AUC], 0.79 for BSI and 0.8 for FACED), but FACED showed slightly superior predictive power for 15-year mortality (AUC, 0.82 for FACED vs. 0.69 for BSI; p=0.0495)[25] likely because age becomes a more important determinant of mortality over longer follow-up time and FACED is more weighted by age. An analysis of seven European cohorts (n=1,612) demonstrated that the BSI accurately predicted hospital admissions, exacerbations, quality of life, respiratory symptoms, 6-minute walk distance, and lung function decline in bronchiectasis while FACED was poorly predictive of most outcomes, although both scoring systems had a good predictive value for mortality[26]. Taken together, both the BSI and FACED (or E-FACED) can precisely predict mortality in bronchiectasis; however, the BSI is more likely to provide a clinically relevant evaluation of overall disease severity compared with FACED.

4. Bronchiectasis Aetiology Comorbidity Index

Understanding the effects of comorbidities on the severity and prognosis of bronchiectasis is essential because of the frequent coexistence of multiple conditions in these patients[27]. The Bronchiectasis Aetiology

Table 2. E-FACED score

Severity marker	Points		
	0	1	2
At least one severe Exacerbation requiring hospitalization in the previous year	No		Yes
FEV_1% predicted	≥50		<50
Age, yr	<70		≥70
Chronic *Pseudomonas* colonization	No	Yes	
Extent (number of lobes)	1–2	>2	
mMRC dyspnea score	0–2	3–4	4

E-FACED risk: 0–3 points, mild; 4–6 points, moderate; 7–9 points, severe.
E-FACED: Exacerbation Added to FACED; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council.

Comorbidity Index (BACI) was developed internally from four European bronchiectasis cohorts (n=986) and externally validated in two independent international cohorts from the United Kingdom (n=88) and Serbia (n=113)[28]. Thirteen comorbidities, including malignancies and chronic obstructive pulmonary disease (COPD), which independently predict mortality rate, were integrated into the BACI. The BACI demonstrated a predictive capability for the 5-year mortality rate, hospital admissions, exacerbations, and health-related quality of life among patients with bronchiectasis. The BACI ranges from 0 to 55 and classifies patients according to BACI scores as low (0), intermediate (1–5), or high (≥6). Distinct differences in outcomes for mortality and hospitalization were observed across the three severity groups. Notably, when the BACI is used in conjunction with the BSI, the combined model is superior to either model alone (Table 3). To aid in calculating the score, an online calculator is provided at http://www.bronchiectasisseverity.com.

Paradigm Shift I: Bronchiectasis Management Focusing on Disease Activity

Although the BSI, E-FACED, and BACI scoring systems have evident value in predicting long-term outcomes in patients with bronchiectasis, most clinical factors comprising severity scores are not reversible or treatable by clinicians. For example, clinicians cannot modify the age or most comorbidities of patients with bronchiectasis. Therefore, while understanding patients at risk of future poor outcomes such as mortality is useful, it may not directly influence many treatment decisions. Furthermore, Asian patients with bronchiectasis frequently show discrepancies in the severity scores and respiratory symptoms. In particular, bronchiectasis patients with TB-destroyed lungs demonstrate multiple lobe involvement on chest CT scans and decreased lung function, which leads to high severity scores; however, they often have mild symptoms and infrequent exacerbation, known as dry bronchiectasis[29].

In this regard, the authors suggest that bronchiectasis treatment practices should focus on disease activity rather than disease severity. Figure 1 illustrates this concept. To illustrate this, we discuss lung damage in terms of a house fire, where the house is the lung, and the fire represents underlying inflammation, infection and mucociliary dysfunction. Bronchiectasis of high disease severity but low activity, usually presenting as extensive lung destruction on chest CT scans but with mild symptoms/infrequent exacerbations, resembles a burnt house that does not require urgent attention because the fire is largely "burnt out." However, bronchiectasis of low disease severity but high activity, usually presenting as radiographically less extensive involvement but high symptom burden plus frequent exacerbations, resembles a house that is actively on fire but still structurally intact and, therefore, requires urgent attention. If appropriate management is provided for bronchiectasis with high activity[12], we may prevent the disease from further lung destruction and consequent disease progression. Therefore, we emphasize a paradigm shift in bronchiectasis management that focuses on disease activity rather than severity. In the next section, we discuss potential methods for measuring disease activity in bronchiectasis, as a single ideal biomarker is not currently available.

Table 3. Bronchiectasis Aetiology and Comorbidity Index

Comorbidity	Score
Metastatic malignancy	12
Hematologic malignancy	6
Chronic obstructive pulmonary disease	5
Cognitive impairment	5
Inflammatory bowel disease	4
Liver disease	4
Connective tissue disease	3
Iron deficiency anemia	3
Diabetes mellitus	3
Asthma	3
Pulmonary hypertension	3
Peripheral vascular disease	2
Ischemic heart disease	2

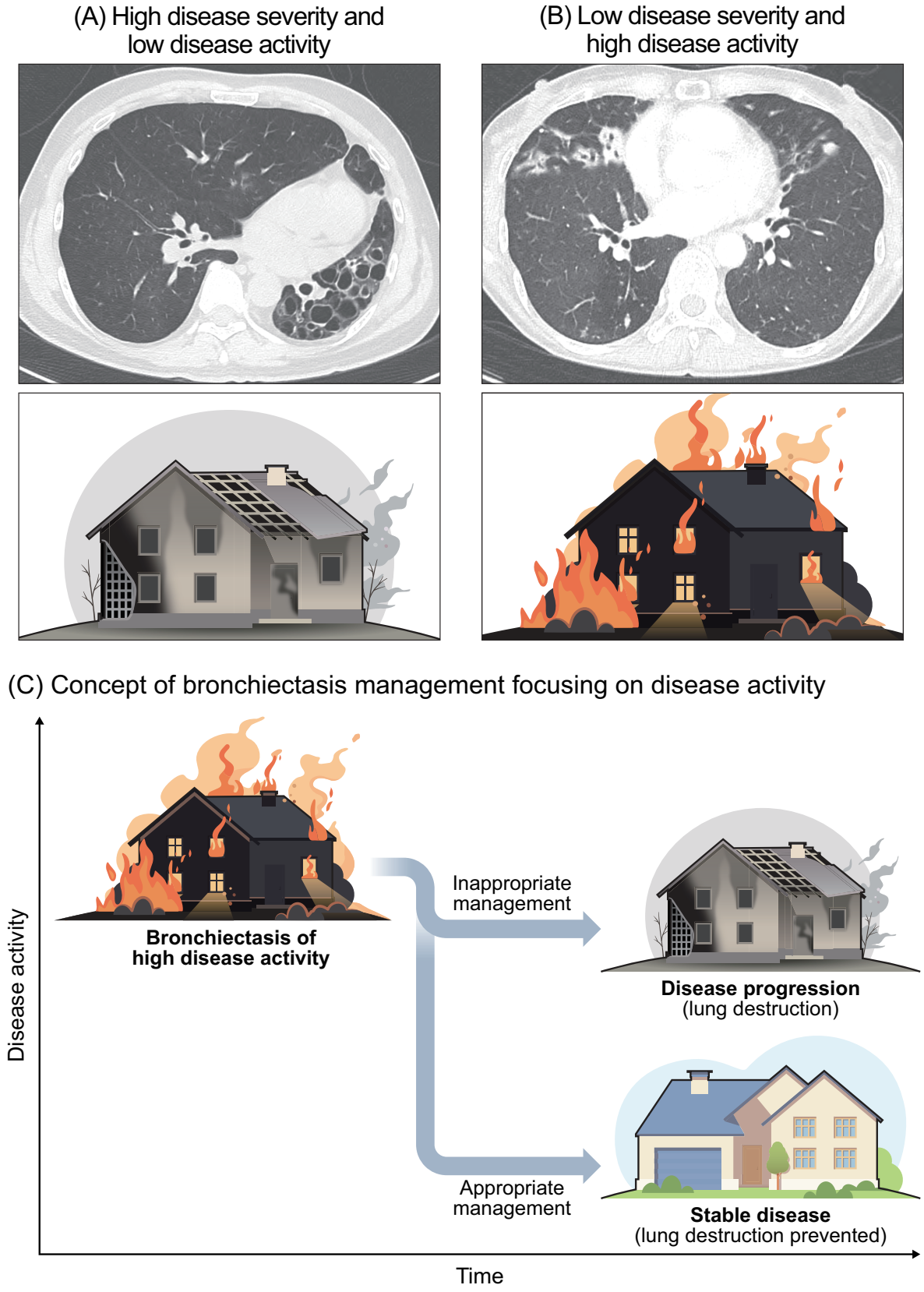
Bronchiectasis Aetiology and Comorbidity Index risk: 0, no high risk comorbidities; 1–6, intermediate risk; ≥6, high risk.

Disease Activity in Bronchiectasis

1. Exacerbations

Bronchiectasis exacerbations are defined as unpredictable worsening of symptoms beyond normal daily variations, which are significant events in the natural course of the disease and determine long-term clinical outcomes[30,31]. A European cohort study categorized 2,572 patients with bronchiectasis into 0, 1, 2, and ≥3 exacerbation per year groups according to the baseline exacerbation frequency and evaluated their long-term clinical outcomes for up to 5 years[32]. Although annual variations in exacerbation frequency existed among the

Figure 1. Concept of bronchiectasis management focusing on disease activity rather than disease severity. (A) Bronchiectasis of high disease severity but low activity, similar to a burnt house. (B) bronchiectasis of low disease severity but high activity, similar to a burning house. (C) Appropriate management should be provided for bronchiectasis of high disease activity to prevent disease progression.



study participants, there was a clear trend that those with more frequent exacerbations at baseline experienced more frequent exacerbations during follow-up. Frequent past exacerbations were the strongest predictors of future exacerbations. The incidence rate ratios for future exacerbation were 1.7 for one exacerbation per year, 3.1 for two exacerbations per year, and 6.0 for ≥3 exacerbations per year at baseline. Furthermore, frequent exacerbators exhibited a poorer quality of life, higher rates of hospitalization, and increased mortality over a 5-year period[32]. These observations underscore the pivotal role of exacerbation in shaping the trajectories of bronchiectasis and disease progression. As discussed later, exacerbations as linked to underlying airway inflammation and may therefore represent a clinically accessible marker of underlying disease activity.

2. Respiratory symptoms

The daily symptom burden may also reflect disease activity in patients with bronchiectasis. Highly symptomatic patients are more likely to experience disease exacerbation and progression. This hypothesis is based on the threshold concept of exacerbations: individuals with more severe daily symptoms would require smaller incremental changes to pass a threshold-prompting treatment and, therefore, are more likely to experience exacerbations[33,34]. To prove this hypothesis, a UK observational cohort study (n=333) analyzed symptoms as either continuous variables or categorized them into high-, moderate-, or low-burden groups (>70, 40–70, and <40) based on the St. George Respiratory Questionnaire (SGRQ) symptom score[33]. The study demonstrated that a 10-point increase in the SGRQ total score corresponded to a higher risk of exacerbation and hospitalization, with a trend toward a shorter time to the first exacerbation. Furthermore, using cutoffs, individuals with high symptom scores exhibited higher risks of exacerbation and hospitalization compared with those with lower scores. Similarly, moderate symptom scores were also associated with a higher hospitalization risk compared with low symptom scores. Therefore, highly symptomatic patients are at an increased risk of exacerbations.

A recently published study reinforced this notion. Gao et al. prospectively included 436 patients with bronchiectasis, evaluated the symptom burden using the Quality-of-Life Bronchiectasis Respiratory Symptom Scale (QoL-B-RSS), and assessed the risk of exacerbation over 12 months[35]. The QoL-B-RSS scores range from 0 to 100, with lower scores indicating more severe symptoms. Remarkably, the baseline QoL-B-RSS score was associated with an increased risk of exacerbations (rate ratio, 1.3 for each 10-point decrease), hospitalizations (rate ratio, 1.2), and reduced time to the first exacerbation (hazard ratio, 1.1) over 12 months, even after adjusting for potential confounders, including exacerbation history. Taken together, the respiratory symptom burden may reflect the future exacerbation risk and disease activity in bronchiectasis.

Symptoms are driven by underlying inflammation, with inflammation being a key driver of mucin release from epithelial cells, and DNA released from inflammatory cells driving mucus viscosity[36,37]. As such, patient symptoms, particularly bronchitis symptoms, are a simple marker of underlying inflammation and disease activity.

3. Sputum color

Among the respiratory symptoms, the authors emphasized sputum color. Patients with bronchiectasis frequently complain of yellowish or green sputum during clinical exacerbations. The distinctive green color of sputum in patients with bronchiectasis results from the accumulation of myeloperoxidase, a green heme-containing protein released from neutrophil granules[38]. Thus, sputum color is considered an indicator of airway inflammation[39,40]. A recent European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) study (n=13,484) demonstrated the clinical significance of sputum color, evaluated by a validated four-point sputum color chart[41], in identifying positive airway bacterial cultures, assessing disease severity, and predicting the risk of future exacerbations[42]. More purulent sputum was robustly correlated with lower FEV_1, worse quality of life, increased bacterial infection, higher BSI score, increased risk of future exacerbations, and mortality during follow-up[42]. Therefore, sputum color is a clinically useful noninvasive biomarker that reflects disease activity in bronchiectasis and identifies patients at risk of future deterioration.

4. Sputum neutrophil elastase and inflammatory profiles

In contrast to sputum color, which indirectly reflects airway inflammation, inflammation was also directly measured by sputum neutrophil elastase (NE), a serine protease contained within azurophilic granules that is elevated in sputum afflicted with neutrophilic inflammatory diseases, such as bronchiectasis and COPD[43]. A UK study measured the sputum NE activity of 381 patients with bronchiectasis at baseline and during exacerbation and assessed long-term clinical outcomes over a 3-year follow-up period[44]. Sputum NE activity was well-correlated with BSI score, mMRC dyspnea

scale score, FEV_1, and the extent of bronchiectasis on chest CT. Moreover, elevated sputum NE activity was associated with a higher frequency of exacerbations during the 3-year follow-up[44]. Hence, sputum NE activity precisely denotes disease activity in bronchiectasis, but its utility may be limited to the usual clinical environment, where a laboratory facility is not equipped. Point-of-care devices for measuring sputum NE activity and myeloperoxidase have been developed for patients with bronchiectasis[45,46]. However, further studies are warranted to determine how lateral flow devices can be used in clinical practice.

Other inflammatory parameters, including elevated levels of eosinophilic inflammation, are associated with exacerbation risk. Patient clusters defined by combined type I and type II inflammation are associated with increased exacerbations, emphasizing the value of inflammatory profiles as a marker of disease activity[47].

5. Mucus plugging on chest computed tomography

The authors suggest that radiological features, particularly mucus plugging on chest CT scans, may serve as indicators of disease activity in bronchiectasis. Based on the authors' clinical experience, patients with bronchiectasis with a high symptom burden frequently exhibit mucus plugging on chest CT scans, which show improvement in the CT features and respiratory symptoms after applying airway clearance techniques and other bronchiectasis management. However, the correlation between mucus plugging and disease activity has been poorly investigated in bronchiectasis compared with that in other chronic respiratory diseases, such as COPD. A recent COPDGene study revealed that mucus plugging was common in patients with COPD, affecting 41% of 4,363 participants[48,49]. Even after adjusting for various factors, including age, sex, race, BMI, smoking history, lung function, and radiological variables, including emphysema, mucus plugging was significantly associated with a higher risk of mortality[48], lung function decline, and exacerbations[49], regardless of the symptoms. Indeed, a recent European multicenter study analyzed CT scans of 524 bronchiectasis patients with a quantitative bronchiectasis scoring technique and investigated the relationships between specific radiological abnormalities and clinical characteristics of bronchiectasis[50]. Interestingly, bronchiectasis patients with *P. aeruginosa* showed a greater degree of mucus plugging[50], which suggested bronchiectasis patients with mucus plugging on chest CT are more likely to have poor outcomes than those without. Nonetheless, future long-term studies are warranted to elucidate this issue in bronchiectasis.

6. Serum C-reactive protein

Serum C-reactive protein (CRP), a simple and highly accessible test, also provides information on the disease activity in bronchiectasis. Two small observational studies measured serum CRP levels in patients with bronchiectasis in a stable state and demonstrated that CRP levels were related to more severe disease in terms of lung function, radiological extent, or disease severity based on the BSI and FACED scores[51,52]. Similarly, a Spanish study (n=802) also measured CRP levels in patients with bronchiectasis during clinically stable periods to assess the value of CRP levels in predicting future exacerbations of bronchiectasis[53]. When the levels were divided into tertiles, patients with bronchiectasis with CRP levels in the second (0.4–2.7 mg/L) and third (≥2.7 mg/L) tertiles presented approximately three- and four-times greater probability, respectively, of experiencing severe exacerbation than the control group (<0.4 mg/L), regardless of bronchiectasis severity or a previous exacerbation history. However, CRP levels cannot predict the occurrence of mild-to-moderate exacerbations[53]. These results suggest that given the pivotal role of airway inflammation in bronchiectasis, biomarkers of systemic inflammation also hold significant importance in the disease[52]. Furthermore, the authors suggest that a subset of patients with bronchiectasis exhibits prominent systemic inflammation but indistinct airway infection[47,54], and patients with this type of inflammation would benefit more from CRP measurement compared with those with other types of inflammation. There are important limitations of systemic inflammatory markers, including confounding from underlying conditions such as connective tissue diseases, which are common in bronchiectasis patients. As such, non-specific systemic inflammatory markers are unlikely to be useful for clinical decision-making in isolation.

Paradigm Shift II: Early Bronchiectasis Management to Prevent Disease Progression

The authors argue that we need to intervene earlier in bronchiectasis patients at high risk of disease progression using the concept of disease activity. Current international guidelines recommend inhaled antibiotics or long-term macrolide therapies in patients with bronchiectasis who experience more than three exacerbations per year[55,56]. In fact, such an approach is effective in averting future exacerbations, but we may miss opportunities to prevent disease progression in some patients with bronchiectasis. Therefore, if bronchiectasis patients exhibit high disease activity even before being

identified as frequent exacerbators, a more proactive preventive approach will preserve function and improve outcomes in bronchiectasis (Figure 1)[57].

Conclusion

Disease severity and activity are both useful in bronchiectasis management; however, they have different values. Disease severity, measured using validated tools, such as the BSI, FACED, and BACI, provides clinicians with information on the long-term outcomes of bronchiectasis. Disease activity, measured using respiratory symptoms and biomarkers, helps clinicians to identify patients more prone to future disease progression in daily clinical practice. Clinicians should recognize patients with bronchiectasis with high disease activity and provide appropriate management early to prevent disease progression.

Authors' Contributions

Conceptualization: Chalmers JD, Choi H. Methodology: all authors. Formal analysis: all authors. Software: all authors. Validation: all authors. Investigation: all authors. Writing - original draft preparation: Im Y, Choi H. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

Yunjoo Im reports no potential conflict of interest relevant to this article. James D. Chalmers reports consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, Insmed, Grifols, Novartis, Boehringer Ingelheim, Pfizer, Janssen, Antabio, and Zambon.

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