Application for Institutional Review Board Approval of Study Protocol

1. Title

Prospective clinical study on Vitamin D replacement in bronchiectasis – A pilot study

2. Investigator

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3. Background

Bronchiectasis refers to a suppurative lung condition characterized by pathological dilatation of bronchi. It is one of the most common chronic airway diseases in Chinese populations (1). The prevalence increased by 2.31-fold between 2013 and 2017 among Chinese urban adults ≥ 18 years (2) . Although there is no official epidemiological report on the prevalence of bronchiectasis in Hong Kong, a local study that validated the diagnostic coding for bronchiectasis in an electronic health record system in Hong Kong recorded 19617 patients with the diagnostic code of bronchiectasis among all public hospitals from 2011 to 2020 (3).

The main pathogenesis of bronchiectasis involves airway inflammation, abnormal mucus clearance, and bacterial colonisation, resulting in progressive airway destruction and distortion. In recent years, evidence suggests a central role of airway inflammation and immune dysregulation in the evolution of bronchiectasis (4). The classic type of airway inflammation is neutrophilic, characterised by abundant neutrophils in sputum and bronchoalveolar lavage fluid, and detected in bronchial biopsy from patients with bronchiectasis, even in a clinically stable-state (5).

Bronchiectasis is also characterized by having micro-organism (bacterial, especially *Pseudomonas aeruginosa* and non-tuberculous mycobacteria) colonization as well as exacerbation. The progressive destruction perpetuates in a vicious cycle, even when the initial insult has subsided. Patients with extensive bronchiectasis present with chronic cough, copious purulent sputum, haemoptysis, progressive loss of lung function, and episodes of infective exacerbations.

Bronchiectasis exacerbation is associated with negative impact on morbidity, mortality, quality of life, and healthcare costs. (6-8) EMBARC Bronchiectasis Registry demonstrated that around 50% of patients had two or more exacerbations annually and one in every three required hospitalizations (9). The prognosis, with respect to hospitalization, mortality and severity, can be predicted by using validated scoring system such as bronchiectasis severity index (BSI) and FACED score (using a combination of forced expiratory volume in the first second (FEV_1), patient's age, the presence of *Pseudomonas aeruginosa* colonization, disease extent and degree of dyspnea to predict five-year all-cause mortality) (10, 11). In addition, health-related quality of life (HRQOL) is severely impaired in bronchiectasis (12).

Vitamin D is known to have immune and inflammatory-modulating effects (13, 14). Both 25(OH)D: calcifediol and its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$: calcitriol), play critical roles in protection against invasive pathogens and reducing risks of autoimmunity. Low 25(OH)D status was reported to increase the susceptibility to infections and developing autoimmunity. According to a systematic review, data strongly suggested that maintaining serum 25(OH)D concentrations of more than 125 nmol/L is associated with significant risk reduction from viral and bacterial infections, sepsis, and autoimmunity (15). Most adequately powered, well-designed, randomized controlled trials with sufficient duration supported substantial benefits of vitamin D. Data confirmed that keeping an individual's serum 25(OH)D concentrations above 125 nmol/L reduces risks from community outbreaks, sepsis, and autoimmune disorders.

There is epidemiological finding of association between vitamin D deficiency and the risk of respiratory tract infections (16, 17). Seasonal vitamin D insufficiency due to reduced sun exposure was reported to be associated with increase in tuberculosis risk (18). Vitamin D deficiency has been associated with worse clinical outcomes in Coronavirus disease 2019 (COVID-19) (19). Vitamin D supplementation was shown to have small effect on reducing the risk of acute respiratory infections compared with placebo (20).

Vitamin D may also play a role in chronic respiratory diseases. High deficiency rate of 25(OH)D was reported to be associated with severity of chronic obstructive pulmonary disease (COPD) (21). Serum vitamin D levels were also inversely associated with COPD risk, severity, and exacerbation (22). Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not with COPD exacerbation. Vitamin D deficiency was associated with a significant decrease in lung function in asthmatic children (23). Supplementation of Vitamin D was reported to improve the indicators of asthma and COPD, especially in pulmonary function, (St. George's Respiratory Questionnaire (SGRQ) scores, interleukin-5 (IL-5), and IgE (24). Vitamin D supplementation can also reduce the rate of asthma exacerbations requiring treatment with systemic corticosteroids (25).

Given the role of vitamin D in immune regulations and the reported infection risks among patients with vitamin D deficiency, it is not surprising that vitamin D deficiency may be linked to poor outcome in bronchiectasis, a disease characterized by chronic bacterial colonization and exacerbation which is mediated through infectious pathogens.

Vitamin D level has been shown to be a good predictor of clinical and radiological severity of bronchiectasis (26, 27). Vitamin-D deficient patients had higher sputum levels of inflammatory markers and demonstrated a more rapid decline in lung function over 3 years follow-up. (28) Vitamin D deficiency is a non-trivial issue in this disease population since as many as 50% were found to be deficient. (28) Colonization rate of *Pseudomonas aeruginosa* were also found to correlate with vitamin D level (21.4% vs. 10.4% vs. 3.6%) in deficient, insufficient and sufficient patients respectively. (28) Vitamin-D deficient patients also had lower predicted FEV_1 by percentage predicted and more frequent pulmonary exacerbations, demonstrating the correlation between exacerbation frequency and vitamin D status (29). Finally, a New Zealand study looked at how Vitamin D supplementation affect the frequency or severity of exacerbations though most patients were not Vitamin D-deficient as baseline. (30). It is important to note that bronchiectasis exacerbation is not the primary outcome of any of the above studies and therefore important confounders such as the intrinsic disease severity or degree of *Pseudomonas aeruginosa* colonization were not properly adjusted in this study.

Limitations do exist in these studies on Vitamin D level and bronchiectasis. Firstly, the studies aforehand mentioned were conducted among Caucasian and middle-east populations (26-29). It has been well reported that the aetiology of bronchiectasis varies greatly across ethnic groups (14). There is also geographical variation in epidemiology and microbiology of bronchiectasis. Secondly, relatively small sample sizes were used in these prior studies.

Our group is also conducting a prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation (UW 22-317) which started in January 2023 and targeted for completion by end of 2024. There were 104 subjects recruited who will be followed up for 12 months. In this ongoing study, 42 (39.3%) of the patients had vitamin D deficiency with baseline vitamin D level below 50 nmol/L. There were 70 patients who completed the interim analysis at 6 months. Patients who are vitamin D deficient had increased risks of developing bronchiectasis exacerbation (10% in Vitamin D deficient group and 0% in vitamin D non-deficient group), p-value = 0.082. Patients who are vitamin D deficient had increased risks of developing hospitalized bronchiectasis exacerbation (13.3% in vitamin D deficient group and 2.5% in vitamin D non-deficient group), p-value = 0.041. Patients with vitamin D deficiency also had higher SGRQ score (symptom domain) [39.4 ± 22.5 vs 28.1 ± 20.4, p = 0.011], SGRQ score (impact domain) [23.6 ± 19.3 vs 16.0 ± 14.9, p = 0.024] and total SGRQ score [29.3 ± 18.1 vs 22.9 ± 15.2, p = 0.063]. The data from this preliminary local pilot data suggested that vitamin D deficiency might have important role in bronchiectasis in terms

of symptom burden and exacerbation risks.

There are several issues and limitations in the previous study on vitamin D supplementation in adults with bronchiectasis (31). Firstly, patients with co-existing respiratory diseases such as asthma in 7 (21%) of the patients were included. This might affect the validity of the results as the benefits of vitamin D supplementation has been shown in prior studies. Secondly, the mean serum 25(OH)D level at baseline before vitamin D supplementation was 70.5 ± 35.3 nmol/L, signifying that a substantial portion of the patients recruited are not vitamin D deficient (defined as serum 25(OH)D level < 50 nmol/L). Some of the outcomes measured are also not bronchiectasis specific. The primary outcome was serum 25(OH)D levels before and after vitamin D3 supplementation, which is indeed unrelated to bronchiectasis. The change in vitamin D level after replacement is rather expected and might not have clinical values in bronchiectasis management. For the secondary outcomes, Dartmouth COOP charts score, SNOT-20 score, Lund–Kennedy score and Leicester cough questionnaire (LCQ) score are all not specific to bronchiectasis. Measuring non-bronchiectasis specific outcomes undermines the ability of the study to assess for the benefits of vitamin D supplementation in bronchiectasis. As bronchiectasis has rather distinct clinical features which are not present in other chronic respiratory diseases (such as haemoptysis), measuring its specific outcomes is critical to assess treatment benefits.

This study therefore seeks to address the limitations in previous related studies on vitamin D replacement and bronchiectasis exacerbation occurrence through a self-controlled pilot study. We aim to investigate whether vitamin D replacement in bronchiectasis patients with vitamin D deficiency can reduce hospitalized bronchiectasis exacerbation occurrence. Patients who participated in the prior study entitled “Prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation” (UW 22-317) will be invited for participation during regular clinic follow-up and management in Queen Mary Hospital. If they are willing to join the further research, they will be recruited in this self-controlled study. There are some differences from usual management to non-CF bronchiectasis subjects. The study subjects would be checked for their blood 25-hydroxyvitamin-D level during the study period. The non-CF bronchiectasis subjects with Vitamin D deficiency would be given 1000 IU and 2000 IU (if needed). We aim to correct their Vitamin D deficiency completely, aiming at blood 25-hydroxyvitamin-D level >=50, i.e. treat to target. The dose depends on the level of Vitamin D after replacement. If blood 25-hydroxyvitamin-D level is 50 or above, then 1000 IU is suffice. If blood 25-hydroxyvitamin-D level is still below 50, we will increase to 2000 IU.

4. Hypothesis

We hypothesize that replacing vitamin D to raise the blood 25-hydroxyvitamin-D level above 50 nmol/L can reduce the occurrence of hospitalized bronchiectasis exacerbation among patients with bronchiectasis and baseline vitamin D deficiency.

5. *Objectives*

To investigate whether vitamin D replacement in bronchiectasis patients with vitamin D deficiency can reduce hospitalized bronchiectasis exacerbation occurrence.

6. *Subject recruitment*

A prospective self-controlled study will be conducted to assess the potential benefits of vitamin D supplementation, aiming at raising the blood 25-hydroxyvitamin-D level above 50 nmol/L.

This study will be conducted at the Department of Medicine, Queen Mary Hospital. The Division of Respiratory Medicine at Queen Mary Hospital is a tertiary referral centre serving the entire territory and is the major receiving unit for patients with various respiratory diseases (including bronchiectasis) in the Hong Kong West Cluster.

Patients who participated in the prior study entitled "Prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation" (UW 22-317) will be invited for participation during regular clinic follow-up and management in Queen Mary Hospital. If they are willing to join the further research, they will be recruited in this self-controlled study. There were 104 subjects in the aforementioned study who will be separated into two groups according to their Baseline blood 25-hydroxyvitamin-D level: vitamin D deficient (below 50 nmol/L) and vitamin D non-deficient (at or above 50 nmol/L). There were initially 42 and 62 patients in the vitamin D deficient and vitamin D non-deficient groups respectively. Patients would be rechecked for 25-hydroxyvitamin-D level to confirm the persistence of deficiency at the recruitment visit.

The following eligibility criteria will apply.

Inclusion criteria: Patients with

1. ages 18 years or above, male or female.
2. confirmed diagnosis of non-CF bronchiectasis based on high-resolution computed tomography (HRCT) scan.
3. participation in the prior study entitled "Prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation" (UW 22-317)

Exclusion criteria: Patients with

1. underlying asthma, COPD and other co-existing respiratory diseases
2. underlying osteoporosis
3. supplementary Vitamin D in their regimen
4. advanced chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30mL/min

7. *Brief outline of methodology*

The following will be performed at the recruitment visit: Detailed medical history (Demographics, duration of bronchiectasis, co-morbidities, exacerbation history), questionnaires (SGRQ, Modified Medical Research Council (mMRC) dyspnoea scale, bronchiectasis impact measure (BIM), Bronchiectasis Health Questionnaire (BHQ)), physical examination, blood tests (Complete blood count, liver and renal function test, 25-hydroxyvitamin-D level, calcium and phosphate level, erythrocyte sedimentation rate, C-reactive protein, high-sensitivity C-reactive protein), and sputum analysis (Bacterial smear and culture, acid fast bacilli smear and culture). The detailed study procedures are summarized in Table 1. The estimated duration for each visit would be 15 minutes.

Outcome measurement

The primary outcome measure is the proportion of patients who develop hospitalized bronchiectasis exacerbation during the follow-up period of 12 months, when compared with the 1-year period before. The Vitamin D deficient group will be compared with their historical data collected in the prior study entitled "Prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation" (UW 22-317) as self-control, as well as the vitamin D non-deficient group.

The secondary outcomes include the change in SGRQ, BIM and BHQ score at 6 and 12 months from baseline, as well as change in number of all/hospitalized bronchiectasis exacerbation in the follow up period of 12 months.

Those with vitamin D deficiency will be replaced with vitamin D3 at 1000 IU at the first visit. Vitamin D3 1000 IU is expected to increase blood 25-hydroxyvitamin-D level by 25 nmol/L. Blood 25-hydroxyvitamin-D level will be rechecked 3 months after replacement. If the blood 25-hydroxyvitamin-D level is still below 50 nmol/L, the vitamin D3 replacement dosage will be increased to 2000 IU. Blood 25-hydroxyvitamin-D level will be checked again at 6 and 12 months.

Patients will be followed up at 3, 6 and 12 months after recruitment. Except for the sputum analysis and blood tests, the same measures in Table 1 will be performed at 6 and 12 months. In addition, patients will be assessed on their bronchiectasis exacerbation record (both bronchiectasis exacerbation managed in an out-patient setting and hospitalized bronchiectasis exacerbation).

Methods

Blood 25-hydroxyvitamin-D level

25-hydroxyvitamin-D will be measured in nmol/L, using in-house liquid chromatography with tandem mass spectrometry (LC/MS-MS) developed by the Department of Chemical Pathology of Queen Mary Hospital. Vitamin D deficiency is defined as 25-hydroxyvitamin-D level below 50 nmol/L, while sufficient vitamin D level is defined as above 50 nmol/L, per the Endocrine Society guidelines (32, 33).

Bronchiectasis exacerbation

Bronchiectasis exacerbation was defined as [1] a deterioration in three or more of the following key symptoms for at least 48 hours, including cough, sputum volume and/or consistency, sputum purulence, dyspnea and/or exercise tolerance, fatigue and/or malaise, hemoptysis AND [2] clinician assessment that a change in bronchiectasis treatment was required usually with administration of antibiotics treatment.

Hospitalized bronchiectasis exacerbations are those exacerbations that fulfil the criteria above and also need at least 24 hours in-patient stay for treatment.

SGRQ

SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease. Consisting of 2 parts with 50 items, it addresses frequency and severity of patients' symptoms as well as activities that cause or are limited by breathlessness. Scores range from 0 to 100, with higher scores indicating more limitations. The minimally important difference is a mean change of 4 units for slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment (34, 35). SGRQ has been validated in patients with bronchiectasis and is considered a valid and sensitive instrument for determining quality of life in bronchiectasis patients (36).

BIM

Bronchiectasis Impact Measure (BIM) is another tool developed to assess patient-reported outcome in bronchiectasis. BIM is a self-administered outcome measure designed to collect patient-perceived health impact at baseline or after a follow-up period in an intervention. It was designed to address some of the perceived limitations of existing tools by being simple (eight items), giving greater scope for a range of responses (10-point visual analogue scale for each item) and by focusing on the impact of disease on quality of life rather than on the frequency or severity of symptoms. BIM consists of eight domains, namely: cough, sputum, breathlessness, tiredness, activity, general health, control, and exacerbations. A score ranges from 0 to 10 for each domain, with 10 being most severe. The total score is 80. BIM has been validated and shown to have excellent internal consistency. The domains were also shown to strongly correlate with bronchiectasis severity and exacerbation history. Statistically significant changes in all BIM domains were observed during an acute exacerbation. PI of this study translated and validated the Traditional Chinese version of BIM in year 2024.

BHQ

BHQ was developed by Spinou et al. (37). Despite the questionnaire's simplicity, the authors concluded that the questionnaire works well in a different population from the development cohort. The instrument comprises 10 questions, each scored on a 7-point scale, to assess quality of life related to bronchiectasis on individuals for a recall period of 2 weeks. The total score ranges from 10 to 70, with a lower score indicating a more negative impact on HRQOL. PI of this study translated and validated the Traditional Chinese version of BIM in year 2024.

Table 1: Study Procedures

	Study Visit			
Visit	**V1**	**V2**	**V3**	**V4**
Months	0	3	6	12
Written informed consent	✓			
Body height, body weight and body mass index	✓			
Medical history and previous medication	✓	✓	✓	✓
Blood samples	✓	✓	✓	✓
Sputum investigation	✓			
Lung function tests	✓			
Blood pressure and pulse measurement	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓
mMRC score	✓		✓	✓
SGRQ score	✓		✓	✓
BIM questionnaire	✓		✓	✓
BHQ questionnaire	✓		✓	✓
Vitamin D replacement (Only for patients with Vitamin D deficiency)	✓ (Dosage: 1000 IU)	✓ (Dosage will be increased to 2000 IU if blood vitamin D level is below 50 nmol/L)	✓	✓

Those with vitamin D deficiency will be replaced with vitamin D3 at 1000 IU at the first visit. Vitamin D3 1000 IU is expected to increase blood 25-hydroxyvitamin-D level by 25 nmol/L. Blood 25-hydroxyvitamin-D level will be rechecked 3 months after replacement. If the blood 25-hydroxyvitamin-D level is still below 50 nmol/L, the vitamin D3 replacement dosage will be increased to 2000 IU. Blood 25-hydroxyvitamin-D level will be checked again at 6 and 12 months. There are some differences from usual management to non-CF bronchiectasis subjects. The study subjects would be checked for their blood 25-hydroxyvitamin-D level during the study period. The non-CF bronchiectasis subjects with Vitamin D deficiency would be given 1000 IU and 2000 IU (if needed). We aim to correct their Vitamin D deficiency completely, aiming at blood 25-hydroxyvitamin-D level >=50, i.e. treat to target. The dose depends on the level of Vitamin D after replacement. If blood 25-hydroxyvitamin-D level is 50 or above, then 1000 IU is suffice. If blood 25-hydroxyvitamin-D level is still below 50, we will increase to 2000 IU.

Patients will be followed up at 3, 6 and 12 months after recruitment. Except for the sputum analysis and blood tests, the same measures in Table 1 will be performed at 6 and 12 months. In addition, patients will be assessed on their bronchiectasis exacerbation record (both bronchiectasis exacerbation managed in an out-patient setting and hospitalized bronchiectasis exacerbation).

Subjects (with justification on the sample size)

Patients who participated in the prior study entitled "Prospective clinical study on serum 25-hydroxyvitamin D (25-OH D) level and risk of bronchiectasis exacerbation" (UW 22-317) will be recruited in this self-controlled study.

There were 104 subjects in the aforementioned study who will be separated into two groups according to their Baseline blood 25-hydroxyvitamin-D level: vitamin D deficient (below 50 nmol/L) and vitamin D non-deficient (at or above 50 nmol/L). There were initially 42 and 62 patients in the vitamin D deficient and vitamin D non-deficient groups respectively.

Data processing and analysis

The demographic and clinical data will be described in actual frequency or mean ± SD, or median and interquartile range, where appropriate.

Baseline demographic and clinical data will be tabulated, as well as compared between Vitamin D deficient and vitamin D non-deficient groups by independent t-test or non-parametric tests where appropriate.

In the Vitamin D deficient group, the proportion of patients with hospitalized bronchiectasis exacerbation before and after vitamin D replacement will be compared by binary logistic regression. The number of all/hospitalized bronchiectasis exacerbation before and after vitamin D replacement will be compared by will be compared with linear regression.

The proportion of patients with all/hospitalized bronchiectasis exacerbation and between vitamin D deficient and vitamin D non-deficient groups will be compared by binary logistic regression. The number of all/hospitalized bronchiectasis exacerbation b between vitamin D deficient and vitamin D non-deficient groups will be compared by will be compared with linear regression.

Covariates including FACED score, age, gender and smoking status will be adjusted in multivariate analysis. For secondary outcome, the change in SGRQ, BIM and BHQ scores at the end of study will be compared between the two groups by linear regression and adjusted for confounders in multivariate analysis. A p-value of <0.05 will be considered statistically significant. All the statistical analyses will be performed using the latest version of Statistical Package for the Social Sciences (SPSS) software.

8. Potential hazards to subjects in the study

Patients will undergo blood tests and breathing (lung function) tests. The breathing tests may be associated with some discomfort, such as chest soreness, shortness of breath and lightheadedness. Pain, bruising or infection may occur from the needle puncture sites. Should patients' non-CF bronchiectasis significantly worsen in the course of the study, study doctor will withdraw them from the study and provide appropriate medical treatment.

Over-replacement of Vitamin D may lead to Vitamin D toxicity which can have the following symptoms: nausea, vomiting, loss of appetite, constipation, dehydration, fatigue, irritability, confusion, weakness and/or weight loss. In this study, the blood serum 25(OH)D level will be checked before the start of Vitamin D replacement and at 3 months after replacement, to ensure the replacement is adequate but not excessive.

9. Confidentiality and use of results

The demographic and clinical data collected from study subjects will be stored securely at the study site for 5 years, with access by the principal investigator or his designated research staff. These data will only be used for the study as outlined in this protocol and individual patient's identity will be removed after completion of statistical analyses.

10. Personal experience of the investigators in the field

The Division of Respiratory Medicine has a strong track record in conducting clinical research on bronchiectasis. Queen Mary Hospital is a well-recognised tertiary referral and research centre in the field of respiratory medicine, with numerous research on bronchiectasis and respiratory diseases conducted therein during the past years. All the investigators are experienced and accredited specialist. Within the last 3 years, the PI (Dr WC Kwok) has served as the first author of 9 out of 10 publications on bronchiectasis.

The current research team (clinical and basic research) under the supervision of the PI consists of 1 senior research assistant, 1 research assistant, 1 technician, and 2 postgraduate students (MPhil). The current research team also has expertise in research related to bone and mineral metabolism.

11. Funding and Conflict of interests

There is no funding received for this study. There will be no conflict of interests from both the department and any of the investigators involved.

12. Declaration

The information supplied above is to the best of our knowledge and belief accurate. We shall comply with the principles enunciated in the present Declaration of Helsinki.

References

1. Gao YH, Lu HW, Mao B, Guan WJ, Song YL, Li YY, et al. The Establishment of China Bronchiectasis Registry and Research Collaboration (BE-China): Protocol of a prospective multicenter observational study. Respir Res. 2022;23(1):328.
2. Feng J, Sun L, Sun X, Xu L, Liu L, Liu G, et al. Increasing prevalence and burden of bronchiectasis in urban Chinese adults, 2013-2017: a nationwide population-based cohort study. Respir Res. 2022;23(1):111.
3. Kwok WC, Tam TCC, Sing CW, Chan EWY, Cheung CL. Validation of diagnostic coding for bronchiectasis in an electronic health record system in Hong Kong. Pharmacoepidemiol Drug Saf. 2023;32(10):1077-82.
4. Boyton RJ, Altmann DM. Bronchiectasis: Current Concepts in Pathogenesis, Immunology, and Microbiology. Annu Rev Pathol. 2016;11:523-54.
5. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. Eur Respir J. 2008;31(2):396-406.
6. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50(3).
7. McDonnell MJ, Aliberti S, Goeminne PC, Restrepo MI, Finch S, Pesci A, et al. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. Lancet Respir Med. 2016;4(12):969-79.
8. Beijers RJ, van den Borst B, Newman AB, Yende S, Kritchevsky SB, Cassano PA, et al. A Multidimensional Risk Score to Predict All-Cause Hospitalization in Community-Dwelling Older

Individuals With Obstructive Lung Disease. J Am Med Dir Assoc. 2016;17(6):508-13.
9. Chalmers JD, Aliberti S, Polverino E, Vendrell M, Crichton M, Loebinger M, et al. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. ERJ Open Res. 2016;2(1).
10. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, Giron RM, Maiz Carro L, de la Rosa Carrillo D, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. Eur Respir J. 2014;43(5):1357-67.
11. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576-85.
12. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015;70(1):12-20.
13. Brumpton BM, Langhammer A, Henriksen AH, Camargo CA, Jr., Chen Y, Romundstad PR, et al. Vitamin D and Lung Function Decline in Adults With Asthma: The HUNT Study. Am J Epidemiol. 2016;183(8):739-46.
14. Chandrasekaran R, Mac Aogain M, Chalmers JD, Elborn SJ, Chotirmall SH. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. BMC Pulm Med. 2018;18(1):83.
15. Wimalawansa SJ. Infections and Autoimmunity-The Immune System and Vitamin D: A Systematic Review. Nutrients. 2023;15(17).
16. Moustaki M, Loukou I, Priftis KN, Douros K. Role of vitamin D in cystic fibrosis and non-cystic fibrosis bronchiectasis. World J Clin Pediatr. 2017;6(3):132-42.
17. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018;1430(1):44-79.
18. Wallis RS, Zumla A. Vitamin D as Adjunctive Host-Directed Therapy in Tuberculosis: A Systematic Review. Open Forum Infect Dis. 2016;3(3):ofw151.
19. Feiner Solis A, Avedillo Salas A, Luesma Bartolome MJ, Santander Ballestin S. The Effects of Vitamin D Supplementation in COVID-19 Patients: A Systematic Review. Int J Mol Sci. 2022;23(20).
20. Jolliffe DA, Camargo CA, Jr., Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9(5):276-92.
21. Zhu B, Zhu B, Xiao C, Zheng Z. Vitamin D deficiency is associated with the severity of COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015;10:1907-16.
22. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity,

and exacerbation: an updated systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2016;11:2597-607.
23. Zhang LL, Gong J, Liu CT. Vitamin D with asthma and COPD: not a false hope? A systematic review and meta-analysis. Genet Mol Res. 2014;13(3):7607-16.
24. Wang Y, Wang J, Chen L, Zhang H, Yu L, Chi Y, et al. Efficacy of vitamin D supplementation on COPD and asthma control: A systematic review and meta-analysis. J Glob Health. 2022;12:04100.
25. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA, Jr., Kerley CP, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017;5(11):881-90.
26. Ferri S, Crimi C, Heffler E, Campisi R, Noto A, Crimi N. Vitamin D and disease severity in bronchiectasis. Respir Med. 2019;148:1-5.
27. Niksarlioglu EY, Kilic L, Bilici D, Yigitbas B, Uysal MA, Camsari G. Vitamin D Deficiency and Radiological Findings in Adult Non-Cystic Fibrosis Bronchiectasis. Turk Thorac J. 2020;21(2):87-92.
28. Chalmers JD, McHugh BJ, Docherty C, Govan JR, Hill AT. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. Thorax. 2013;68(1):39-47.
29. Sami R, Zohal M, Marhamati KA, Rajabi S, Shokri-Mashhadi N. 25-Hydroxy vitamin D and body composition are associated with pulmonary function in non-cystic fibrosis bronchiectasis: A cross-sectional study. Clin Nutr ESPEN. 2021;46:527-31.
30. Bartley J, Garrett J, Camargo CA, Jr., Scragg R, Vandal A, Sisk R, et al. Vitamin D3 supplementation in adults with bronchiectasis: A pilot study. Chron Respir Dis. 2018;15(4):384-92.
31. Bartley J, Garrett J, Camargo CA, Jr., Scragg R, Vandal A, Sisk R, et al. Vitamin D(3) supplementation in adults with bronchiectasis: A pilot study. Chron Respir Dis. 2018;15(4):384-92.
32. Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012;196(11):686-7.
33. Paxton GA, Teale GR, Nowson CA, Mason RS, McGrath JJ, Thompson MJ, et al. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. Med J Aust. 2013;198(3):142-3.
34. Jones PW. Quality of life, symptoms and pulmonary function in asthma: long-term treatment with nedocromil sodium examined in a controlled multicentre trial. Nedocromil Sodium Quality of Life Study Group. Eur Respir J. 1994;7(1):55-62.
35. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J. 2002;19(3):398-404.
36. Chan SL, Chan-Yeung MM, Ooi GC, Lam CL, Cheung TF, Lam WK, et al. Validation of the Hong Kong Chinese version of the St. George Respiratory Questionnaire in patients with

bronchiectasis. Chest. 2002;122(6):2030-7.
37. Spinou A, Siegert RJ, Guan WJ, Patel AS, Gosker HR, Lee KK, et al. The development and validation of the Bronchiectasis Health Questionnaire. Eur Respir J. 2017;49(5).