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RESEARCH ARTICLE

CT score and correlation with lung function and microbiology of adult patients with cystic fibrosis with predominant I1234V genotype in Qatar

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ABSTRACT

Background: Computed tomography (CT) features of cystic fibrosis (CF) lung disease can be objectively quantified using current CT scoring systems to assess the extent and severity of the disease. The aims of this study were to calculate the Santamaria CT scores in adult patients with CF with the predominant CFTR I1234V genotype, determine its reliability, and correlate these parameters with lung function, microbial colonization, compliance to treatment, and exacerbations.

Methodology: This retrospective observational study was conducted on adult patients with CF who were regularly followed up in the adult CF service at Qatar via CT scans that were taken not during an acute exacerbation. CT scans were scored using the Santamaria scoring system. Corresponding spirometry, microbiological data of sputum culture, and relevant clinical data were correlated with individual CT scores.

Results: Only 23 of the 31 patients underwent CT when not in an acute exacerbation and were included in the study analysis. A total of 20 (87%) patients had the I1234V genotype. There was good agreement between the two radiologists on the Santamaria CT scores with an intraclass correlation coefficient (ICC) value of 0.991. Bronchiectasis was the most consistent finding, followed by interlobular and intralobular septal thickening. Patients with poor lung function and frequent exacerbations had significantly higher CT scores ($p = 0.015$). The CT scores of patients colonized with *Pseudomonas aeruginosa* were higher but nonsignificant ($p = 0.20$). The mean CT scores were significantly higher in patients who

were noncompliant to regular treatment than in those who were compliant ($p = 0.012$).
Conclusion: Santamaria CT scores comprise a reliable scoring system for adult patients with CF and can be used to determine the extent and severity of lung disease. *P. aeruginosa* colonization causes more structural lung damage than other common colonizing organisms. Noncompliance to treatment has a significant impact on the increasing severity of CF lung disease.

Keywords: Cystic fibrosis, CT score, lung function, microbiology

INTRODUCTION

In cystic fibrosis (CF), lung disease is the cause of major morbidity and mortality because of chronic infection and inflammation.[1] Recurrent lung infections and colonization occur at an early age with *Staphylococcus aureus* and *Haemophilus influenzae* and subsequently with the mucoid phenotype of *Pseudomonas aeruginosa*.[2] Chronic infection with *P. aeruginosa* has clearly been associated with decreased lung function, worsening of structural damage, and higher morbidity and mortality in patients with CF.[3] Although the gold standard to objectively categorize deterioration is the pulmonary function test (PFT), the only approved surrogate end point,[4] computed tomography (CT) scoring systems can also quantify structural abnormalities in CF in a reproducible manner.[5–7] Several CT scoring systems, including the Bhalla, Santamaria, Brody, and Helbich, have been developed, utilized, and critically investigated.[8] Compared with the Brody and Bhalla scoring systems, the Santamaria scoring system has been particularly shown to be superior in terms of providing more clinically relevant information, while being more versatile and easy to use, as demonstrated in a previous study on patients with CF in Qatar.[9]

The CFTR I1234V mutation is one of the common mutations found in the Arabian Gulf and belongs to a large kindred Arab tribe, consisting of a number of families who share a common ancestry and culture. It is the predominant mutation among patients with CF in Qatar.[10] An earlier study had examined pediatric and adult patients with the CFTR I1234V genotype in Qatar to assess the efficacy of scoring systems compared with PFT.[9] Because that study included both adult and pediatric patients, we cannot ascertain whether the scores are representative of a particular age category. Moreover, that study compared CT scores with PFT and included patients aged 2 years onward, although PFTs were performed for patients aged only ≥ 6 years. In view of these findings, we conducted a study to reliably highlight the important features in adult patients with CF using CT scores, lung function, and sputum microbiology. The purpose of this study was to determine the CT scores in only adult patients with CF in Qatar with a focus on the predominant I1234V genotype. The primary outcome was to assess the reliability of the Santamaria scoring system and to determine its relationship with lung function and the colonization pattern. The secondary outcome was to correlate the CT scores with compliance to treatment and exacerbations.

METHODOLOGY

This retrospective observational study was conducted from January 2010 to March 2017 at the tertiary center Hamad General Hospital in Qatar. A total of 31 patients were regularly followed up under the adult CF service during this period. All patients were aged >18 years. Although all patients underwent CT, only 23 patients underwent CT at least once while not in an acute exacerbation. These 23 patients were included in the present study.

High-resolution computed tomography (HRCT), spirometry, microbiological data of routine sputum culture, and relevant clinical data inclusive of demographics, body mass index, medical record documentation of compliance, and number of exacerbations in a year warranting inpatient admission to address the objectives of the study were collected by a review of electronic medical records on an approved data collection form.

The findings of HRCT performed during the study period when the patient was "stable" were included in this study. Patients were defined as stable when there was no exacerbation in documentation or by spirometry (near-normal baseline FEV1).
An exacerbation is defined as new or increased cough, sputum production, dyspnea with exertion or rest, increased fatigue, decreased appetite, change in sputum appearance, fever, and/or an isolated drop in FEV1 $>10\%$ from baseline.
Patients with more than two exacerbations per year requiring inpatient admission were labeled as frequent exacerbators, whereas those with two or less than two inpatient admissions were labeled as infrequent exacerbators.

Current scanning protocols in our institution incorporate the lungs from the apex to the base using a 64-slice capability multidetector CT (MDCT). End inspiratory scans of 1-mm thickness with 8-mm intervals are obtained using the following parameters: 100 kV, variable mA (40 – 60 mA), and 0.6 seconds of scanning time. Two radiologists independently reviewed and scored the CT scans using the parameters listed in the Santamaria scoring system. The total score for all parameters summed up to 27. The parameters were severity and extent of bronchiectasis, peribronchial thickening, generations of bronchial division involved (bronchiectasis/plugging), number of bullae, air trapping, collapse, thickening of intra – inter lobular septa, acinar nodules/consolidation, and ground-glass opacities. Scores from 0 to 3 were assigned for each bronchial and parenchymal abnormality, with 0 indicating normal and 3 representing the most severe abnormality with intervening mild to moderate grades. A higher score denotes a more severe CF lung disease.

Spirometry was performed using the standard protocol recommended by the American Thoracic Society.[11] Data included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximum expiratory flow at 50% and 25% of vital capacity (FEF_{25-75}). Results were described as the percentage of the predicted values based on reference values of PFT. Patients were divided into four groups, severe, moderate, mild, and normal, based on the FEV1 results; FEV1: $<40\%$, FEV1: 40% – 69%, FEV1: 70% – 89%, and FEV1: $\geq 90\%$, respectively. $FEF_{25\%-75\%}$ was considered as reflective of small airways and categorized as normal if $FEF_{25\%-75\%} \geq 60\%$ and severe if $FEF_{25\%-75\%} < 20\%$.[12]

The routine outpatient treatment in the management of adult patients with CF involves nebulized medications, including dornase alfa, hypertonic saline, and chest physiotherapy, to enhance airway clearance with or without prophylactic antibiotics. The compliance of patients to the prescribed medications and instructions was gathered from physician documentation in electronic medical records. Patients were labeled to be complaint if they followed the physician's instructions and prescriptions on most days of the week for all medications and instructions. Compliance to treatment was documented and described by the physician in the clinic CF care template.

Statistical analysis

All data are expressed as mean, standard deviation, or frequencies. Statistical analysis was performed using the SPSS package (SPSS Inc, Chicago, U.S.A.). Intra-rater reliability of CT scores was assessed using the intraclass correlation coefficient (ICC). Unpaired *t*-test and the nonparametric Mann – Whitney U test as appropriate were applied for nonparametric comparisons between two groups, and the Kruskal – Wallis test was applied for

Table 1. Demographics.

Characteristic	N (%)
Sex	
Male	12 (52)
Female	11 (48)
Mean age, years	26.3 ± 6.2 years
Nationality	
Qatar	21 (91.3)
Saudi Arabia	2 (8.7)
Genotype	
Homozygous I1234v/I1234v	20 (87)
Others	3 (13)
Mean BMI, kg/m^2	26 ± 5.7
Colonization	
Mucoid *Pseudomonas aeruginosa*	18 (78.2)
Staphylococcus aureus	18 (78.2)
Haemophilus influenzae	11 (47.8)

Table 2. CT scores in relation to lung function-FEV1, FEF_{25-75} (N = 23).

	CT score Radiologist 1		CT score Radiologist 2	
FEV1	Mean ± SD	Median ± Range	Mean ± SD	Median ± Range
≥90%	7.3 ± 4.1	4 ± 0	8 ± 4.6	4.5 ± 1
70%–89%	10 ± 5.9	9 ± 13	10.4 ± 5.4	10 ± 13
40%–69%	12.1 ± 3.8	14 ± 16	11.5 ± 3.8	14 ± 15
<40%	21 ± 0	21 ± 0	21 ± 0	21 ± 0
Overall *p* value	0.056		0.063	
$FEF_{25\%-75\%}$				
≥60%	6.8 ± 5.4	4 ± 14	7.1 ± 5.19	4.5 ± 13
40%–59%	12.4 ± 5.0	14 ± 16	12.2 ± 4.7	14 ± 15
20%–39%	12.2 ± 4.2	14 ± 9	12.7 ± 3.9	14 ± 9
<20%	21 ± 0	21 ± 0	21 ± 0	21 ± 0
Overall *p* value	0.043		0.036	

nonparametric comparisons among three groups. The chi-square (χ^2) test was used to analyze and examine the association between two or more categorical variables. The relationships between CT scores and pulmonary function parameters were examined using Pearson's and Spearman's correlation coefficients. A p value <0.05 was considered to be statistically significant.

RESULTS

The clinically stable cohort of adult patients with CF in our study had a mean age of 26.3 ± 6.2 years, ranging from 18 to 42 years, with a nearly equal male: female ratio (Table 1). The CT scores of the 20 patients with the confirmed I1234V/I1234V genotype were 10.8 ± 5.8 and 11 ± 5.9 as evaluated by the first and second radiologists, respectively. The mean CT score of the entire cohort evaluated by the first radiologist was 11.7 ± 5.9 and that evaluated by the second radiologist was 11.8 ± 5.6, with excellent interobserver agreement evidenced by the intraclass correlation coefficient (ICC) 0.992 (95% CI 0.981–0.997). Bronchiectasis (100%) was the most common finding, followed by thickening of intralobular and interlobular septae in 18 (78.2%) patients and peribronchial thickening in 17 (73.9%) patients. Patients with a high bronchiectasis score had a mean total CT score of 16.2 ± 12. Presence of bullae was noted in 5 (21.7%) patients, and this increased the mean CT score to 20.5 ± 4.

Relationship between CT scores and lung function

Patients with severely reduced lung function had a significantly high mean CT score of 21 ± 0 compared with those with normal lung function (6.9 ± 4.3) ($p = 0.02$) (Table 2). Furthermore, patients with severely reduced FEF_{25-75} had a significantly higher mean CT score of 21 than patients with normal FEF_{25-75} with a mean CT score of 6.9 ± 5.4 ($p = 0.015$). There was a significant negative correlation between mean CT scores and FEV1 (−0.677), FEF_{25-75} (−0.599), and FVC (−0.595) (Table 3).

Relationship of CT scores with colonization, compliance to treatment, and exacerbations

P. aeruginosa was of the mucoid phenotype in all patients. Although statistically nonsignificant, the CT

Table 3. Correlation of lung function to CT scores (N = 23).

	CT score radiologist 1		CT score radiologist 2	
Variable	Correlation coefficient (*r*)	*p* value	Correlation coefficient (*r*)	*p* value
FEV1	−0.677	<0.0001	−0.661	0.001
FVC	−0.595	0.003	−0.566	0.005
FEF_{25-75}	−0.599	0.003	−0.614	0.002

Table 4. CT scores based on microbiology (N = 23).

Organism	Mean CT score	Median CT score	*p* value
Noncolonized (N = 2)	6.00 ± 2.8	6 ± 4	
Pseudomonas (N = 18)	12.7 ± 5.7	14.5 ± 18	0.20
Non-*Pseudomonas* (N = 5)	9.2 ± 6	6.5 ± 11	
Staphylococcus aureus (N = 15)	11.4 ± 6.2	10 ± 18	0.70
Non-*Staphylococcus aureus* (N = 6)	12.5 ± 5.6	14 ± 17	

scores were numerically higher in patients colonized with *Pseudomonas* (12.7 ± 5.7) than in patients without *Pseudomonas* (9.2 ± 6) ($p = 0.20$). The CT scores were similar in relation to *S. aureus* colonization (Table 4).

Sixteen (51.6%) patients were not compliant with the routine recommended treatment (Table 5). The mean CT scores were significantly higher (14.3 ± 5.7) in patients who were noncompliant to regular treatment than in those who were compliant (8.4 ± 4.0) ($p = 0.012$). The mean CT scores in infrequent exacerbators (8.7 ± 4.6) were significantly lower than those in frequent exacerbators (14.1 ± 4.5) ($p = 0.05$).

DISCUSSION

CT scoring involves establishing the presence, extent, and severity of CT features of CF lung disease. Although all scoring systems have demonstrated consistent and comparable results, we used the Santamaria scoring system as it has more clinically important observations related to small airway and was the preferred method in a study conducted previously in pediatric and adult patients with CF with the I1234v mutation.[9] In our study, the interobserver agreement calculations revealed that the Santamaria scoring system is highly reproducible. Commonly observed structural abnormalities included bronchiectasis, peribronchial thickening, and mucus plugging. Bronchiectasis was the most consistent finding observed in all patients. Total CT scores were found to be higher in patients with a greater extent of bronchiectasis, suggesting that the assessment of disease severity could be deduced from the degree or extent of bronchiectasis on CT. In a study conducted by De Jong et al. in 119 patients with CF, it was concluded that peripheral bronchiectasis score was the most "sensitive" outcome parameter that can be used in clinical studies as it showed the largest annual change among CT composite scores, individual component scores, and certain lung function parameters.[13] The presence of bullae was also associated with an overall increased score, averaging up to 20.5, which points toward an increased severity of the lung disease.

Traditionally, FEV1 has been used as the best surrogate for survival (a true outcome measure) and for monitoring the course of CF lung disease.[14] However, CT may be superior at identifying early lung damage in patients with CF and more accurately represents disease burden than FEV1 as it can pick up abnormalities such as mild bronchiectasis or a mosaic attenuation pattern even when FEV1 is normal.[15,16] Scores derived from CTs have been shown to correlate well with PFTs and clinical findings.[5,8] In our study, there was an inverse correlation between FEV1 and FVC scores and FEF_{25-75} scores with the CT score. A previous study conducted in adult and pediatric patients with homozygous I1234V mutation also reported similar findings of negative correlation between spirometry variables and Santamaria CT scores.[9] In the subset of 60 patients from the Pulmozyme Early Intervention Trial with HRCT and PFT, the partial Spearman's correlations were significant with FEV1 (−0.46; $p = 0005$) and $FEF_{25\%-75\%}$ (−0.36; $p = 0.0076$) and, although nonsignificant, had a negative correlation with FVC (−0.25; $p = 0.0609$).[17] However, recent studies have demonstrated that CT scores are more sensitive

Table 5. Relationship of CT scores with compliance to treatment and exacerbations per year requiring inpatient admissions (N = 23).

Compliance	Mean CT scores	*p* value
Compliant (N = 13)	8.4 ± 4.0	0.012
Not Compliant (N = 10)	14.3 ± 5.7	
Exacerbations (per year)		
≤2 (N = 7)	8.7 ± 4.6	0.05
>2 (N = 16)	14.1 ± 4.5	

than PFTs in detecting and monitoring the onset and progression of CF lung disease.[13,18] This highlights the fact that a higher CT score can denote a lower lung function and escalation of clinical care should be considered.

The decline in pulmonary function is secondary to the progressive impairment of airway conductance, and the primary proven culprit is chronic *P. aeruginosa* infection that causes epithelial surface damage and airway plugging. In addition to causing an acute decline in lung function, pulmonary exacerbations are known to cause long-term deterioration in lung function.[19] This fact has been validated in our study where the CT scores were found to be generally higher in patients with a greater number of exacerbations (Table 5). Therefore, the necessity for exacerbations to be treated promptly and aggressively is paramount. Our study has shown that CT scores are higher in *Pseudomonas*-colonized patients, whereas there was no difference in scores with *S. aureus* colonization. However, this difference was not significant because of the small study population. This difference is not surprising considering that the irreversible, structural bronchopulmonary lesion of bronchiectasis was significantly related only to the colonization with mucoid *P. aeruginosa* in comparison with other risk factors (*S. aureus*, *H. influenzae*, and antibiotic use) in a study involving 82 patients with CF evaluating 12 risk factors for developing irreversible lesions (such as bronchiectasis).[20] Similar findings were also noted in a retrospective study on 41 patients with CF from Brazil where the Bhalla CT scores were significantly higher in the group of patients infected with *P. aeruginosa* than in the group of patients infected with *S. aureus*, thereby reinforcing the well-known association between colonization with *P. aeruginosa* and disease progression.[21] Therefore, early treatment of nonmucoid *P. aeruginosa* with antibiotics capable of eradicating this organism before mucoid transformation occurs is clearly desirable to prevent the early development of progressive lung disease with bronchiectasis, especially in children with CF.[22]

Current treatment modalities in CF target the downstream consequences. These include mucolytic agents (e.g., dornase alfa), airway surface hydration (e.g., hypertonic saline), anti-infective agents given for prophylaxis, eradication, suppression, and during episodes of acute exacerbation.[23] The importance of adherence to medication on health outcomes in patients with CF has been much emphasized and investigated because of the significant clinical impact on lung health outcomes in case of poor compliance.[24] Therapeutic adherence was found to worsen with age and disease severity in a study conducted by Arias et al.[25] In general, patients with poor compliance to respiratory medications had higher CT scores in our study (Table 2). Therefore, it is important to reinforce the importance of adherence in every clinic visit. Moreover, noncompliance to routinely recommended treatment was observed in more than half of the patients, stressing the need to address the reasons, be it psychosocial, treatment-related, or lack of understanding of the nature of the disease.

The limitations of this study are those inherent of any retrospective investigation. The small number of adult patients with CF prevents us from generalizing the study results to all patients with this genotype. This study on adult patients with CF in Qatar with the predominant I1234V genotype highlights that CT score can be considered as an objective marker in assessing the severity of CF lung disease as it correlates with lung function. It also signifies the importance of intensively treating patients colonized with *Pseudomonas* and to improvise these treatment modalities to improve compliance.

Declaration of Conflict of Interest

This manuscript is an original one. It has not been published or considered for publication elsewhere. None of the authors has financial or otherwise any conflict of interest from publishing this manuscript. The manuscript has been seen and agreed upon by all authors.

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Authors' Contributions

MT: contributed to the conception and design of the study, data analysis and interpretation, and manuscript writing and review and gave the final approval for publication

MR: contributed to the conception and design of the study, data analysis, and drafting of the manuscript and gave the final approval for publication

MA: contributed to data analysis, interpretation, and drafting and review of the manuscript and gave the final approval for publication

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PC: contributed to data analysis, interpretation, and drafting and review of the manuscript and gave the final approval for publication

MA: contributed to the conception and design of the study, data analysis, and drafting of the manuscript and gave the final approval for publication

Ethical approval

This study was approved by the Medical Research Centre, Hamad Medical Corporation RP, #17105/17.

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REFERENCES

1. Flume PA, O'Sullivan BO, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey- Courand DB, Finder J, Lester M, Quittell L, Rosenblatt R. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2007;176(10): 957 – 969.
2. Burns JL, Emerson J, Stapp JR, Yim DL, Krzewinski J, Louden L, Ramsey BW, Clausen CR. Microbiology of sputum from patients at cystic fibrosis centers in the United States. *Clin Infect Dis.* 1998;27(1): 158 – 163.
3. Rosenfeld M, Ramsey BW, Gibson RL. Pseudomonas acquisition in young patients with cystic fibrosis: pathophysiology, diagnosis, and management. *Curr Opin Pulm Med.* 2003;9(6):492 – 497.
4. Danders DB, Li Z, Brody AS. Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis. *Annals ATS.* 2015;12(1):64 – 69.
5. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP. Cystic fibrosis: scoring system with thin-section CT. *Radiology.* 1991; 179(3):783 – 788.
6. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol.* 1999; 29(10):731 – 735.
7. Santamaria F, Grillo G, Guidi G, Rotondo A, Raia V, de Ritis G, Sarnelli P, Caterino M, Greco L. Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? *Pediatrics.* 1998;101(5): 908 – 913.
8. de Jong PA, Ottink MD, Robben SGF, Lequin MH, Hop WCJ, Hendriks JJE, Pare PD, Tiddens HAWM. Pulmonary disease assessment in cystic fibrosis: Comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology.* 2004;231:434 – 439.
9. Bhat V, Wahab AA, Garg KC, Janahi I, Singh R. HRCT in cystic fibrosis in patients with CFTR I1234V mutation: Assessment of scoring systems with low dose technique using multidetector system and correlation with pulmonary function tests. *Indian J Radiol Imaging.* 2015;25(1):44 – 51.
10. Abdul Wahab A, Dawod ST, al Thani G. Cystic fibrosis in a large kindred family in Qatar. *Ann Trop Paediatr.* 2000;20(3):203 – 207.
11. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med.* 1995;152(3):1107 – 1136.
12. UK Cystic Fibrosis Registry Annual Data Report 2012.
13. de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, Tiddens HA. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. *Thorax.* 2006;61(1):80 – 85.
14. Loeve M, Krestin GP, Rosenfeld M, de-Bruijne M, Stick SM, Tiddens HA. Chest computed tomography: a validated surrogate endpoint of cystic fibrosis lung disease? *Eur Respir J.* 2013;42(3):844 – 857.
15. Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Gotz M, Wojnarowski C, Brasch RC, Herold CJ. Cystic fibrosis: CT assessment of lung involvement in children and adults. *Radiology.* 1999;213(2): 537 – 544.
16. Brody AS. Early morphologic changes in the lungs of asymptomatic infants and young children with cystic fibrosis. *J Pediatr.* 2004;144(2):154 – 161.
17. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: Distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr.* 2004;145(1):32 – 38.
18. de-Jong PA, Nakano Y, Lequin MH, Mayo JR, Woods R, Paré PD, Tiddens HA. Progressive damage on high resolution computed tomography despite stable lung

function in cystic fibrosis. *Eur Respir J.* 2004;23(1): 93 – 97.

19. Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. *Pediatr Pulmonol.* 2011;46: 393 – 400.
20. Farrell PM, Collins J, Broderick LS, Rock MJ, Li Z, Kosorok MR, Laxova A, Gershan WM, Brody AS. Association between mucoid Pseudomonas infection and bronchiectasis in children with cystic fibrosis. *Radiology.* 2009;252(2):534 – 543.
21. Folescu TW, Marques ED, Boechat MC, Daltro P, Higa LY, Cohen RW. High-resolution computed tomography scores in cystic fibrosis patients colonized with Pseudomonas aeruginosa or Staphylococcus aureus. *J Bras Pneumol.* 2012;38(1):41 – 49.
22. Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Döring G, von-der-Hardt H. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol.* 1998;25(2): 88 – 92.
23. Edmondson C, Davies JC. Current and future treatment options for cystic fibrosis lung disease: latest evidence and clinical implications. *Ther Adv Chronic Dis.* 2016;7(3):170 – 183.
24. Eakin MN, Riekert KA. The impact of medication adherence on lung health outcomes in cystic fibrosis. *Curr Opin Pulm Med.* 2013;19(6):687 – 691.
25. Arias LRP, Bousoño GC, Díaz MJJ. Treatment compliance in children and adults with cystic fibrosis. *J Cyst Fibrosis.* 2008;7(5):359 – 367.