Original Research

Clinical Implications of *Pseudomonas Aeruginosa* Colonization in Chronic Obstructive Pulmonary Disease Patients

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***Running Head: Pseudomonas Aeruginosa* Colonization in COPD Patients**

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Abbreviations:

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Abstract

BACKGROUND:

Pseudomonas aeruginosa is an important pathogen in patients with chronic respiratory diseases. It can colonize the airway and could have prognostic value in bronchiectasis and cystic fibrosis. Its role in chronic obstructive pulmonary disease (COPD) is less well defined.

METHODS:

A prospective study was conducted in Hong Kong to investigate the possible association between *Pseudomonas aeruginosa* colonization and acute exacerbation of COPD (AECOPD) risks.

RESULTS:

Among 327 Chinese patients with COPD included, 33 (10.1%) of the patients had *Pseudomonas aeruginosa* colonization. Patients with or without *Pseudomonas aeruginosa* colonization had similar background characteristics. Patients with *Pseudomonas aeruginosa* colonization had increased risks of moderate to severe AECOPD, severe AECOPD and pneumonia with adjusted odds ratio (aOR) of 3.15 (95% CI 1.05 – 9.48, p = 0.042), 2.59 (95% CI 1.01 – 6.64, p = 0.048) and 4.19 (95% CI 1.40 – 12.54, p = 0.011) respectively. Patients with *Pseudomonas aeruginosa* colonization also had increased annual frequency of moderate to severe AECOPD, median 0 [0 – 0.93] in the non-*Pseudomonas aeruginosa* colonization group and 1.35 [0 – 3.39] in the *Pseudomonas aeruginosa* colonization group, with a p-value of 0.005 in multi-variate linear regression.

CONCLUSION:

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Pseudomonas aeruginosa colonization is a potential independent risk factor for moderate to severe AECOPD and pneumonia among patients with COPD without co-existing bronchiectasis.

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Background

*Pseudomonas aerug*inosa is a Gram-negative bacteria reported to have significant prognostic value in chronic respiratory diseases including cystic fibrosis and bronchiectasis [1-4]. Epidemiological studies showed an increasing trend of antimicrobial resistance, including multi-drug resistant (MDR) isolates in recent years[5]. *Pseudomonas aeruginosa* is well known to persist which is attributed to its ability to form antibiotic-resistant biofilms [6]. As such, *Pseudomonas aeruginosa* can persist in the airway as a bacterial colonizer. *Pseudomonas aeruginosa* can also lead to airway inflammation and secondary lung damage, resulting in worsening clinical status and progressive disease[7]. In recent years, *Pseudomonas aeruginosa* has also been recognized to be an important micro-organism in patients with chronic obstructive pulmonary disease (COPD)[8,9]. *Pseudomonas aeruginosa* can be isolated in up to 15% of patients with COPD[10]. *Pseudomonas aeruginosa* colonization was found to be more commonly seen in patients with more severe COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, with mucoid strains more frequently seen in advanced COPD[11]. Patients with exacerbator phenotype, active smokers, patients who had prior admission to an Intensive Care Unit, patients who received several courses of antibiotics or systemic corticosteroids and those with the concomitant bronchiectasis were also at risk of *Pseudomonas aeruginosa* isolation[12]. Patients with *Pseudomonas aeruginosa* isolated during exacerbation or upon follow-up had more frequent exacerbations, more severe airflow limitation and higher mortality[13]. *Pseudomonas aeruginosa* can have different manifestations in patients with COPD, including as a colonizer which has variable duration of persistence, causing acute exacerbations and it may also cause chronic infection[14]. The dose of inhaled corticosteroid (ICS) was also found to be a potential risk factor for *Pseudomonas aeruginosa* infection in patients with severe COPD. Despite this, the

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role of *Pseudomonas aeruginosa* in COPD remains inconclusive. There are still debates on whether *Pseudomonas aeruginosa* reflects disease severity in COPD or *Pseudomonas aeruginosa* causes the accelerated deterioration of COPD. Hence, we conducted the current study to investigate the clinical implications of *Pseudomonas aeruginosa* colonization in patients with COPD.

Methods

A prospective study was conducted at Queen Mary Hospital (QMH) and Grantham Hospital (GH), which are tertiary respiratory referral centres in the Hong Kong West Cluster. Chinese patients aged at or above 40, with at least 10 pack years of smoking history, and COPD followed up in QMH or GH in the year 2021 were prospectively recruited from the respiratory specialty clinic in QMH/GH at their routine follow-up for COPD, with the recruitment done at their clinical stable state. The diagnosis of COPD was confirmed by spirometry demonstrating post-bronchodilator airflow limitation with forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio less than 70%, in line with the latest recommendation in GOLD[15]. Notably, co-existing asthma, bronchiectasis and interstitial lung disease were excluded. The diagnosis of bronchiectasis was confirmed if it meets the international consensus recommendations on the criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults[16]. Written informed consent was obtained from the patient at the time of recruitment. History taking, physical examination and blood taking for a complete blood count would be performed at the time of recruitment. Sputum microbiology results of the patients included from year 2021 to 2022 were retrieved. The relevant medical records including demographic data, clinical data /investigations, and use of medication records were recorded during the recruitment visit. Regular use of ICS, long-acting beta-agonists (LABA), long-acting

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muscarinic antagonists (LAMA), theophylline and roflumilast was defined as the continuous use for at least 12 months prior to recruitment. *Pseudomonas aeruginosa* colonization was defined as the persistence of *Pseudomonas aeruginosa* in repeated (≥3) sputum specimens or bronchoalveolar lavage taken at a stable state without clinical evidence of infection and tissue damage[17].

Acute exacerbation of COPD (AECOPD) was defined using the latest GOLD recommendation. AECOPD was defined as an acute event characterized by worsening respiratory symptoms beyond normal day-to-day variations, leading to a change in medications. Such symptoms would include one or more of the following: [1] increased cough frequency and severity; [2] increased sputum volume and/or changed sputum character; [3] increased dyspnoea that required medical attention and treatment [15]. Mild AECOPD was defined as AECOPD that was treated with short-acting bronchodilators only. Moderate AECOPD was defined as AECOPD that was treated with short-acting bronchodilators and oral corticosteroids. Severe AECOPD was defined as AECOPD that was treated requiring hospitalizations or emergency department visits [15]. Clinical stable state was defined as free from AECOPD and any systemic corticosteroid use by more than 90 days. Patients were continued on the standard-of-care treatment from the primary team in charge. The patients were prospectively followed up after recruitment into the study in the respiratory/COPD specialty clinic in QMH/GH every 16 to 26 weeks for the symptoms, COPD control, medication compliance, any AECOPD and the date of the first exacerbation, until 31st December 2023.

The primary outcome was the development of any moderate to severe AECOPD. The secondary outcomes include the development of any severe AECOPD, any severe AECOPD that required invasive or non-invasive mechanical ventilation, the annual number of moderate to severe

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AECOPD, the annual number of severe AECOPD, the development of pneumonia, the development of extra-pulmonary complications (acute coronary syndrome and ischaemic stroke), and the overall survival.

This study was approved by The University of Hong Kong and Hospital Authority Hong Kong West Cluster Institutional Review Board (approval reference number: UW 21-172).

Statistical analysis

The demographic and clinical data were described in actual frequency, mean ± standard deviation (SD) or median [inter-quartile range (IQR)]. Baseline demographic and clinical data were compared between the two groups (with or without *Pseudomonas aeruginosa* colonization) with independent t-tests or non-parametric tests where appropriate. To identify the association between *Pseudomonas aeruginosa* colonization and the development of moderate to severe/severe AECOPD/severe AECOPD that required invasive or non-invasive mechanical ventilation, development of pneumonia and extra-pulmonary complications (acute coronary syndrome and ischaemic stroke), univariate logistic regression analyses were performed. Multiple logistic regression modelling was used to assess for covariates. Age, gender, body mass index, baseline FEV_1, COPD assessment test (CAT) scale, number of AECOPD in the year before subject recruitment, use of relevant medications (ICS, LAMA, LABA) and baseline blood eosinophil count were adjusted as covariates. These covariates were adjusted as they were factors that were reported to be associated with risks of AECOPD. Multi-variable linear regression was performed to assess the association between *Pseudomonas aeruginosa* colonization and annual number of moderate to severe AECOPD/severe AECOPD. Cox regression analysis was used to

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assess the survival. Fields with $p < 0.05$ are regarded as statistically significant at 2-sided test. All statistical analyses were done using the 28th version of SPSS statistical package.

Results

There were 366 patients with COPD followed up in QMH/GH being screened in this study. 12 patients with history of asthma, 6 with ILD and 21 with bronchiectasis were excluded. The patient selection was illustrated in Figure 1. 327 patients were included in the final analysis.

Baseline characteristics

The mean age was 74.5 ± 8.9 years, with male predominance (91.1%). The mean FEV_1 was 1.40 ± 1.34 L (63 ± 23% predicted). The mean CAT score was 9.5 ± 7.7. Among these 327 patients included, 33 (10.1%) of them had *Pseudomonas aeruginosa* colonization. 10 (3.1%) of the patients had *Moraxella catarrhalis* colonization and 42 (42.8%) had Haemophilus influenzae colonization. Patients with or without *Pseudomonas aeruginosa* colonization had similar background characteristics except for a higher number of AECOPD in the past 1 year before recruitment. The results are summarized in Table 1. The mean follow-up duration was 1.94 ± 0.48 years.

Moderate to severe AECOPD

172 (52.6%) of the patients had moderate to severe AECOPD in the follow-up period. 24 (72.7%) in the *Pseudomonas aeruginosa* colonization group and 148 (50.3%) in the non-*Pseudomonas aeruginosa* colonization group had moderate to severe AECOPD in the follow-up period (Figure 2). The odds ratio (OR) was 2.63 (95% confidence interval [CI] 1.18 – 5.85, p = 0.018) for the *Pseudomonas aeruginosa* colonization group. The adjusted OR (aOR) was 3.15

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(95% CI 1.05 – 9.48, p = 0.042) suggesting increased risks of severe AECOPD in the *Pseudomonas aeruginosa* colonization group.

The median annual moderate to severe AECOPD frequency was 0 [0 – 0.93] in the non-*Pseudomonas aeruginosa* colonization group and 1.35 [0 – 3.39] in the *Pseudomonas aeruginosa* colonization group, with p-value of 0.005 in multi-variable linear regression.

Severe AECOPD

108 (33.0%) of the patients had severe AECOPD in the follow-up period. 17 (51.5%) in the *Pseudomonas aeruginosa* colonization group and 91 (31.0%) in the non-*Pseudomonas aeruginosa* colonization group had severe AECOPD in the follow-up period (Figure 3). The OR was 2.37 (95% CI 1.15 – 4.90, p = 0.020) for *Pseudomonas aeruginosa* colonization group. The aOR was 2.59 (95% CI 1.01 – 6.64, p = 0.048) suggesting increased risks of severe AECOPD in the *Pseudomonas aeruginosa* colonization group.

The median annual severe AECOPD frequency was 0 [0 – 0.46] in the non-*Pseudomonas aeruginosa* colonization group and 0.43 [0 – 1.31] in the *Pseudomonas aeruginosa* colonization group, with p-value of 0.064 in multi-variable linear regression.

Severe AECOPD that required invasive or non-invasive mechanical ventilation

24 (7.3%) of the patients had severe AECOPD that required invasive or non-invasive mechanical ventilation in the follow-up period with 4 (12.1%) in the *Pseudomonas aeruginosa* colonization group and 20 (6.8%) in the non-*Pseudomonas aeruginosa* colonization group. The OR was 1.89 (95% CI 0.61 – 5.91, p = 0.27) for *Pseudomonas aeruginosa* colonization group.

Pneumonia

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38 (11.6%) of the patients had pneumonia in the follow-up period with 8 (24.2%) in the *Pseudomonas aeruginosa* colonization group and 30 (10.2%) in the non-*Pseudomonas aeruginosa* colonization group. The OR was 2.82 (95% CI 1.17 – 6.80 p = 0.02) for *Pseudomonas aeruginosa* colonization group. The aOR was 4.19 (95% CI 1.40 – 12.54, p = 0.011) suggesting increased risks of pneumonia in the *Pseudomonas aeruginosa* colonization group.

Among the patients who developed pneumonia, 10 (33.3%) in the non-*Pseudomonas aeruginosa* colonization group had pneumonia due to *Pseudomonas aeruginosa* and 20 (66.7%) had pneumonia caused by other micro-organisms.

Among the patients who developed pneumonia, 3 (37.5%) in the *Pseudomonas aeruginosa* colonization group has pneumonia due to *Pseudomonas aeruginosa* and 5 (62.5%) had pneumonia caused by other micro-organisms.

Extra-pulmonary complications

3 (0.9%) of the patients developed acute coronary syndrome in the follow-up period with none in the *Pseudomonas aeruginosa* colonization group and 3 (1.0%) in the non-*Pseudomonas aeruginosa* colonization group. 3 (0.9%) of the patients developed acute coronary syndrome in the follow-up period with none in the *Pseudomonas aeruginosa* colonization group and 3 (1.0%) in the non-*Pseudomonas aeruginosa* colonization group.

Mortality

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67 (20.5%) died in the follow-up period with 7 (21.2%) in the *Pseudomonas aeruginosa* colonization group and 60 (20.4%) in the non-*Pseudomonas aeruginosa* colonization group. There was statistical difference in the mortality risks in the 2 groups, with hazard ratio of 1.06 (95% CI = 0.48 – 2.32, p = 0.89) for the *Pseudomonas aeruginosa* colonization group.

Discussion

In this study, the prognostic role of *Pseudomonas aeruginosa* colonization was demonstrated. *Pseudomonas aeruginosa* colonization was shown to be an independent risk factor for future AECOPD, including moderate to severe AECOPD and severe COPD, as well as pneumonia. The importance of *Pseudomonas aeruginosa* colonization in COPD should not be underestimated.

Pseudomonas aeruginosa is one of the most important bacterial pathogens in chronic respiratory diseases. In bronchiectasis, *Pseudomonas aeruginosa* was shown to be associated with increased inflammation, greater impairment of lung function, more exacerbations, increased mortality and a deterioration of life quality[1,18,19]. Its ability to form biofilms provides *Pseudomonas aeruginosa* with an enormous advantage to establish infections[20]. Because of its prognostic value in bronchiectasis, *Pseudomonas aeruginosa* colonization was included in different score systems for severity assessment of bronchiectasis, including Bronchiectasis Severity Index (BSI)[21], FACED score (FEV_1, percentage predicted (F), age (A), presence of chronic colonization by *P. aeruginosa* (C), radiologic extension (E) and dyspnoea (D)[22] and the E-FACED score (FACED plus exacerbations)[23] . Chronic bacterial infection and colonization are also being recognized in COPD [24]. However, one limitation in prior studies is that patients with co-existing bronchiectasis were also included, in which *Pseudomonas aeruginosa* is commonly colonizing

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the airway in bronchiectasis [25,26]. Hence, to understand the burden and clinical implications of bacteria, in particular *Pseudomonas aeruginosa* colonization in patients with COPD without co-existing respiratory diseases.

In our study, patients with *Pseudomonas aeruginosa* colonization were shown to have increased risks of moderate to severe, severe AECOPD and pneumonia. This concurs with previous reports on the negative impact of *Pseudomonas aeruginosa* colonization in COPD and other respiratory diseases. While *Pseudomonas aeruginosa* eradication was recommended in bronchiectasis, there has been a lack of evidence on that in COPD and this remains a clinical controversy [10].

The association of *Pseudomonas aeruginosa* colonization and AECOPD risks can be explained by the nature of *Pseudomonas aeruginosa* and its effect on the airway. First of all, *Pseudomonas aeruginosa* can form biofilm, which is antibiotic-resistant and offer protection for the bacteria towards, subsequently allowing colonization in the airway [6]. *Pseudomonas aeruginosa* was also shown to contribute to airway inflammation and epithelial damage in bronchiectasis [4,27]. *Pseudomonas aeruginosa* colonization was also shown to be a risk factor for bronchiectasis exacerbation[2]. These properties of *Pseudomonas aeruginosa* as demonstrated in other diseases such as bronchiectasis could contribute to the observed AECOPD risks in our study. By colonizing the airway in patients with COPD, this leads to chronic airway inflammation, which eventually results in AECOPD. And AECOPD itself is one of the most important risk factors for future AECOPD [28]. *Pseudomonas aeruginosa* colonization can serve as the trigger for the vicious cycle in COPD. Once colonized in the airway, it is difficult to be eradicated and leads to the inflammatory cascade with AECOPD being the final outcome.

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In our study, we did not demonstrate the relationship with ICS use, including the dose and type of ICS to be associated with risks of *Pseudomonas aeruginosa* colonization. In prior study, ICS dose was reported to be associated with increased risks of *Pseudomonas aeruginosa* colonization[13]. In order to properly examine this association, a larger sample size may be needed. This possible association is worth further study as ICS use has been demonstrated to be associated with pneumonia risks in COPD, especially for fluticasone [29]. On the other hand, ICS use was shown not to augment further the already increased risk of hospitalization for pneumonia associated with concomitant bronchiectasis in patients with COPD [30]. Nonetheless, safe initiation of ICS should be executed in patients with COPD especially among those with *Pseudomonas aeruginosa* colonization given their elevated AECOPD risks.

While we excluded patients with known bronchiectasis in our study, it will be interesting to know if *Pseudomonas aeruginosa* colonization among COPD patients is linked to future risks of developing bronchiectasis. Further studies are required to find out whether COPD patients colonized with *Pseudomonas aeruginosa* in their airways are more likely to develop bronchiectasis compared with those colonized with other organisms.

Our study has several limitations. Firstly, the study was conducted in two tertiary centres and we may miss those patients with mild COPD that are managed in the primary care setting. Yet, those with milder COPD are also less likely to have AECOPD and pneumonia, which are the primary and secondary outcomes of our study. Secondly, not all patients had high-resolution computed tomography of the thorax (HRCT) done to exclude bronchiectasis. The authors reviewed all chest radiographs (CXR) with radiologists reporting the chest radiograph. This may underestimate the number of cases of bronchiectasis that were excluded. As *Pseudomonas aeruginosa* colonization predominantly occurs in patients with more severe bronchiectasis, and

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all patients with *Pseudomonas aeruginosa* colonization had HRCT and/or CXR reviewed to be without definite bronchiectasis, this limitation would be a relatively minor one. To further validate the findings of this study, a larger scale study with HRCT done in all subjects should be conducted.

Conclusion

Pseudomonas aeruginosa colonization is an independent risk factor for moderate to severe AECOPD and pneumonia among patients with COPD without co-existing bronchiectasis.

Declaration of Interests

- Ethics approval and consent to participate

  This study protocol was reviewed and approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (IRB/ REC Ref: UW 21-172). Written informed consent was obtained from the patient at the time of recruitment.

- Competing interests

  The authors have no conflicts of interest to declare.

- Authors' contributions

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Dr Wang Chun Kwok was involved with study concept and design, analysis and interpretation of data, acquisition of data, drafting of manuscript, and approval of the final version of the manuscript. Dr Terence Chi Chun Tam and Chi Hung Chau were involved with critical revision of the manuscript for important intellectual content and approval of the final version of the manuscript. Dr James Chung Man Ho was involved with the study concept and design, drafting of manuscript, critical revision of the manuscript for important intellectual content, study supervision, and approval of the final version of the manuscript.

- Data Availability Statement

  Research data are not shared.

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Table 1 Baseline demographic and clinical characteristics

	Whole cohort (n = 327)	*Pseudomonas aeruginosa* colonization absent (n = 294)	Presence of *Pseudomonas aeruginosa* colonization (n = 33)	P-values
Age (years), mean ± SD	74.5 ± 8.9	74.3 ± 8.8	76.6 ± 9.2	0.18
Male (%)	297 (91.1%)	268 (91.2 %)	30 (90.9%)	0.96
BMI (kg/m^2), mean ± SD	23.1 ± 4.6	23.2 ± 4.6	22.0 ± 4.4	0.16
CAT score, mean ± SD	9.5 ± 7.7	9.4 ± 7.7	9.8 ± 7.5	0.79
FEV_1 (L), mean ± SD	1.40 ± 0.57	1.42 ± 0.55	1.25 ± 0.71	0.22
FEV_1 (% predicted), mean ± SD	62.6 ± 22.7	63.2 ± 22.5	56.6 ± 24.5	0.17
FVC (L), mean ± SD	2.82 ± 0.86	2.83 ± 0.85	2.65 ± 0.94	0.33
FVC (% predicted), mean ± SD	92.8 ± 24.8	93.2 ± 25.2	89.1 ± 20.4	0.35
FEV_1/FVC ratio (%), mean ± SD	50.8 ± 15.8	51.2 ± 16.1	46.6 ± 12.4	0.07
Number of exacerbation(s) in the past 1 year, mean ± SD	0.14 ± 0.57	0.12 ± 0.51	0.33 ± 0.92	0.04*
Number of exacerbation(s) in the past 1 year (%)				0.04*
0	298 (91.1%)	270 (91.8%)	28 (84.8%)	
1	21 (6.4%)	19 (6.5%)	2 (6.1%)	

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2	4 (1.2%)	3 (1.0%)	1 (3.0%)	
≥ 3	4 (1.2%)	2 (0.7%)	2 (6.1%)	
Length of stay of exacerbation(s) in the past 1 year, mean ± SD	8.5 ± 8.6	7.8 ± 8.6	11.6 ± 8.4	0.4
Blood eosinophil count at bassline (x cells/µL), mean ± SD	241 ± 200	241 ± 209	240 ± 183	0.97
LABA use (%)	240 (73.4%)	211 (71.8%)	29 (87.9%)	0.075
LAMA use (%)	262 (80.1%)	234 (79.6%)	28 (84.8%)	0.47
ICS use (%)	159 (48.6%)	141 (48.0%)	18 (54.5%)	0.47
Long term oxygen therapy (%)	54 (16.5%)	46 (15.6%)	8 (24.2%)	0.21
Home non-invasive ventilation (%)	5 (1.5%)	4 (1.4%)	1 (3.0%)	0.08
Co-morbidities (%)				
Hypertension	136 (41.6%)	123 (41.8%)	13 (39.4%)	0.79
Diabetes mellitus	52 (15.9%)	47 (16.0%)	5 (15.2%)	0.90
Ischaemic heart disease	53 (16.2%)	50 (17.0%)	3 (9.1%)	0.24
History of stroke	7 (2.1%)	7 (2.4%)	0 (0%)	0.37
History of malignancies	56 (17.1%)	47 (16.0%)	9 (27.3%)	0.10

SD = standard deviation; mL = millilitre; * = statistically significant; BMI = body mass index; CAT = Chronic obstructive pulmonary disease assessment test; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity, LABA = long-acting beta-agonists, LAMA = long-acting muscarinic antagonists, ICS = inhaled corticosteroid,

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Figure 1 Patient selection flow diagram

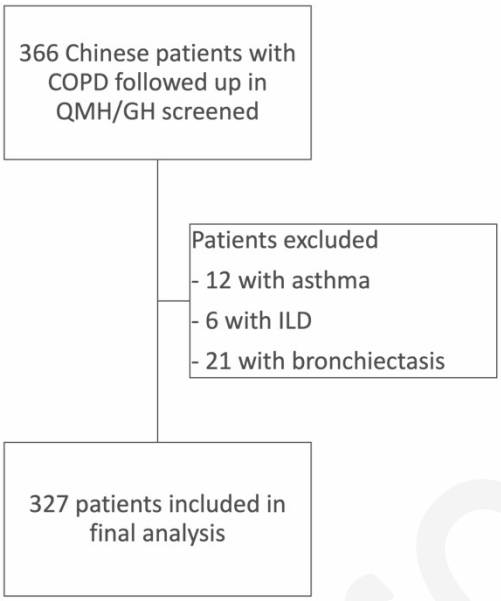

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Figure 2 Percentage of patients with moderate to severe AECOPD

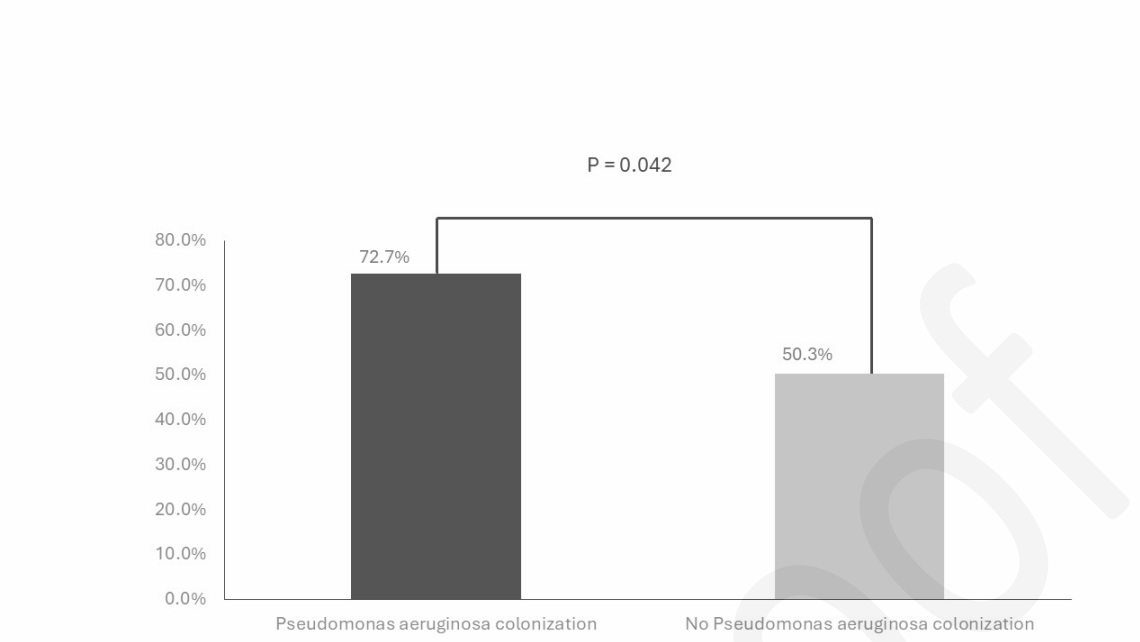

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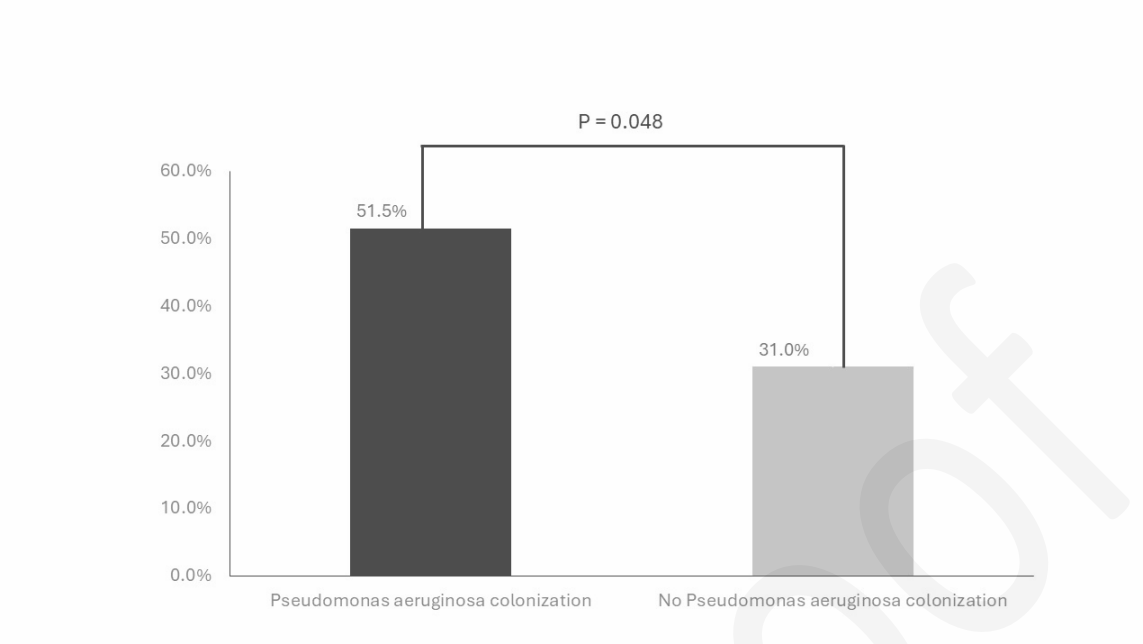
Figure 3 Percentage of patients with severe AECOPD



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