

Predictors of pneumonia on routine chest radiographs in patients with COPD: a post hoc analysis of two 1-year randomized controlled trials

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Background: Patients with COPD are at risk for life-threatening pneumonia. Although anatomical abnormalities in the thorax may predispose to pneumonia, those abnormalities identified on routine chest X-rays (CXRs) in patients with COPD have not been studied to better understand pneumonia risk.

Methods: We conducted a post hoc exploratory analysis of data from two replicate year-long clinical trials assessing the impact of fluticasone furoate–vilanterol versus vilanterol alone on COPD exacerbations (GSK studies: HZC102871/NCT01009463 and HZC102970/NCT01017952). Abnormalities on baseline CXRs from 179 patients who developed pneumonia and 50 randomly selected patients who did not were identified by blinded consensus readings conducted by two radiologists. Positive and negative likelihood ratios and diagnostic odds ratios (ORs) were calculated to evaluate the markers for subsequent pneumonia development during the 1-year study period.

Results: Baseline characteristics distinguishing the pneumonia and non-pneumonia groups included a lower body mass index (24.9 vs 27.5 kg/m², $P=0.008$), more severe airflow obstruction (mean post-bronchodilator forced expiratory volume in 1 second [FEV₁]/forced vital capacity ratio: 42.3% vs 47.6%, $P=0.003$), and prior pneumonia (36% vs 20%, $P=0.030$). Baseline CXR findings with the highest diagnostic ORs were: elevated hemi-diaphragm (OR: 6.87; 95% CI: 0.90, 52.26), thick tracheal-esophageal stripe (OR: 4.39 [0.25, 78.22]), narrow cardiac silhouette (OR: 2.91 [0.85, 9.99]), calcified pleural plaque/mid-chest pleural thickening (OR: 2.82 [0.15, 53.76]), and large/prominent pulmonary artery shadow (OR: 1.94 [0.95, 3.97]). The presence of a narrow cardiac silhouette at baseline was associated with a statistically significant lower mean pre-bronchodilator FEV₁ ($P=0.040$). There was also a trend for a lower mean pre-bronchodilator FEV₁ in patients with a large/prominent pulmonary artery shadow at baseline ($P=0.095$).

Conclusion: Findings on routine CXR that relate to pathophysiological mechanisms of pneumonia could help determine pneumonia risk in patients with COPD.

Keywords: COPD, pneumonia, chest X-rays, predictors of risk

Introduction

COPD is more commonly associated with pneumonia compared with other chronic diseases.¹ Patients with COPD are at an increased risk of developing community-acquired pneumonia (CAP)²⁻⁴ – a phenomenon thought to be linked to altered host innate immune mechanisms leading to susceptibility for pathogen colonization.⁵ The risk of developing CAP appears to be elevated with an increasing airflow limitation severity of COPD.^{6,7} A retrospective, UK population-based cohort study of 40,414 patients with COPD estimated the overall incidence of CAP at 22.4 episodes/1,000

person-years; corresponding rates were 18.2, 19.2, and 35.9 episodes/1,000 person-years in patients with mild, moderate, and severe COPD, respectively.⁶ Furthermore, a US-based longitudinal study reported higher rates of pneumonia hospitalizations in patients with more severe COPD; rates were 22.7/1,000 person-years in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3/4 compared with 6.9, 6.0, and 2.9/1,000 person-years in those with GOLD stages 2, 1, and 0 (normal lung function), respectively.⁷ Moreover, there are data to suggest that patients with COPD are at an increased risk of pneumonia-associated mortality. A retrospective, observational study of 744 hospitalized patients with CAP reported significantly higher 90-day mortality rates in patients with COPD, compared to those without (18.6% vs 11.7%; $P=0.013$).⁸ Thus, predicting pneumonia risk in patients with COPD is of clinical importance.

Aside from severe airflow obstruction,⁹ factors associated with increased pneumonia risk in patients with COPD include low body mass index (BMI),^{5,9} older age,^{5,6} use of psychoanaleptics,⁹ presence of gastroesophageal reflux disease (GERD),¹⁰ and use of inhaled corticosteroids (ICS).⁵ Furthermore, the presence of anatomical abnormalities in the lung or thorax could render the airway parenchyma prone to respiratory infection^{11–13} or reflect underlying disease severity.

The chest radiograph (chest X-ray; CXR) is the most common clinical test used to screen for such anatomical abnormalities; however, other than in cystic fibrosis,¹⁴ very little is known about how CXR findings in patients with chronic respiratory diseases, including COPD, might relate to the subsequent risk of developing pneumonia. An opportunity to retrospectively assess this risk is possible by utilizing baseline CXRs collected during clinical trials in COPD.

To investigate whether abnormalities detected on routine CXRs could be associated with subsequent pneumonia development in patients with COPD, we conducted a post hoc analysis of data from two previously published randomized controlled trials that assessed the effect of the ICS/long-acting β_2 agonist (LABA) combination of fluticasone furoate (FF) plus vilanterol (VI) versus VI alone in preventing exacerbations of COPD.¹⁵

Methods

This post hoc exploratory analysis of the association between baseline CXR findings and subsequent development of pneumonia was conducted using data from two replicate multicenter, double-blind, parallel-group, 1-year, randomized

controlled trials that evaluated the effect of once-daily FF (50, 100, or 200 μg) plus VI 25 μg versus VI 25 μg alone on the prevention of exacerbations of COPD (NCT01009463 and NCT01017952).¹⁵ The trial protocols were approved by relevant institutional review boards/independent ethics committees, details of which are provided in the Supplementary Materials. The trials were conducted in accordance with Good Clinical Practice guidelines and the principles founded in the Declaration of Helsinki. All patients provided written informed consent.¹⁵

The trial population comprised outpatients aged ≥ 40 years with a diagnosis of COPD, who had a smoking history of ≥ 10 pack-years, a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio ≤ 0.70 after bronchodilators, a post-bronchodilator $\text{FEV}_1 \leq 70\%$ of predicted, and a documented history of ≥ 1 moderate/severe exacerbations of COPD in the previous year. Baseline CXRs (posterior–anterior and lateral views) were obtained at screening. Adverse events of pneumonia were coded per MedDRA version 14.1. In total, 3,255 patients were randomized to treatment across the two studies; of these, 181 developed pneumonia during the 1-year study period. All but two patients who developed on-treatment pneumonia had a baseline CXR available for independent radiologic review as part of this study.

The objective of the present analysis was to compare baseline CXR findings in patients who developed on-treatment pneumonia ($n=179$; pneumonia group) with a randomly selected subset of patients who did not ($n=50$; non-pneumonia group).

A subjective qualitative review of all 229 baseline CXRs was first undertaken by a pulmonologist (D.B.R.) and an infectious disease specialist (D.V.G), with both physicians blinded to treatment arm and chronological identity of the images. CXR findings were categorized into 21 groups according to pre-specified definitions (normal posterior–anterior and lateral views from COPD patients are shown in Figure 1A and B, respectively): 1) abnormal cardio/thoracic ratio measurement; 2) atelectasis or other evidence of volume loss; 3) basilar lines of COPD; 4) blurring or loss of diaphragmatic shadow; 5) calcified pleural plaque over the diaphragm (on posterior–anterior view) or mid-chest pleural thickening (Figure 1C); 6) elevation of hemi-diaphragm (indirect sign of volume loss [any lobe]) (Figure 1D); 7) evidence of hiatal hernia; 8) focal or diffuse reticular-nodular or “ground glass” shadows; 9) hyperinflated chest; 10) indirect signs of upper lobe volume loss (right hilum equal to left hilum position, right upper lobe atelectasis, and/or elevation of minor fissure on posterior–anterior view); 11) large cardiac

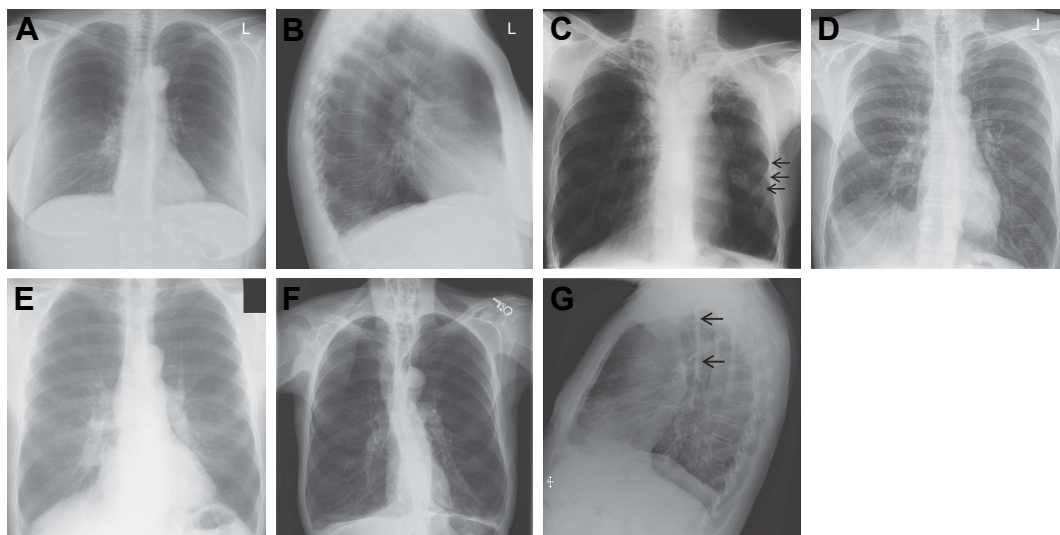


Figure 1 CXR findings in patients with COPD.

Notes: (A) Normal posterior–anterior view of hyperinflated chest; (B) normal lateral view of hyperinflated chest; (C) calcified pleural plaque/mid-chest pleural thickening; (D) elevated hemi-diaphragm; (E) large/prominent pulmonary artery shadow; (F) narrow cardiac silhouette; and (G) thick tracheal-esophageal stripe.

Abbreviation: CXR, chest X-ray.

silhouette; 12) large/prominent pulmonary artery shadow along the right mainstem bronchus (Figure 1E); 13) narrow cardiac silhouette (Figure 1F); 14) normal heart size in a hyperinflated chest (normal cardiac silhouette); 15) pleural thickening (any pleural change); 16) pleural thickening at apices; 17) pleural thickening at bases including costophrenic angle blunting; 18) signs of bronchiectasis; 19) signs of congestive heart failure including basilar effusion and Kerley B lines; 20) thick tracheal-esophageal stripe on lateral view (Figure 1G); and 21) vascular calcifications: coronary, carotid, or aortic.

A blinded independent subjective qualitative review of all CXRs was then conducted by two radiologists (H.A. and M.O.), who reviewed the CXR films together and determined a final interpretation of CXR findings by reaching a consensus.

The pneumonia and non-pneumonia groups were statistically compared for a variety of parameters: Student's *t*-test was used for between-group comparisons of mean values for age, BMI, and lung function parameters at screening. Between-group differences in the proportions of patients with/without a particular CXR finding or medical history were tested using the chi-square test or Fisher's exact test (the latter was used if cell values were <5). Positive likelihood ratios (LR+), negative likelihood ratios (LR–), and diagnostic odds ratios (OR) were also calculated. No adjustments were made for other baseline factors in these analyses. Similar analyses were conducted using history of pneumonia as a potential predictive marker.

Results

Patient demographics and baseline characteristics are summarized in Table 1. Compared with the non-pneumonia group, patients in the pneumonia group had a significantly lower mean BMI (24.9 vs 27.5 kg/m²; *P*=0.008) and mean post-bronchodilator FEV₁/FVC ratio (42.3% vs 47.6%;

Table 1 Patient demographics and baseline characteristics

Patient characteristics	Pneumonia group (n=179) ^a	Non-pneumonia group (n=50) ^b	<i>P</i> -value ^c
Mean age (SE), years	64.0 (0.69)	63.8 (1.34)	0.880
Male/female, n (%)	107 (60)/72 (40)	26 (52)/24 (48)	ND
Mean BMI (SE), kg/m ²	24.9 (0.47)	27.5 (0.74)	0.008
Ethnicity, n (%)			
Hispanic or Latino	15 (8)	13 (26)	
Other	164 (92)	37 (74)	ND
Geometric mean post-bronchodilator FEV ₁ (% CV), L	1.11 (37.47)	1.18 (32.62)	0.245
Mean post-bronchodilator FEV ₁ /FVC ratio (SE), %	42.3 (0.83)	47.6 (1.66)	0.003
Percent predicted post-bronchodilator FEV ₁ (SE), %	41.7 (0.99)	45.2 (1.72)	0.096

Notes: Statistically significant *P*-values (*P*≤0.05) are shown in bold. ^aOriginal treatment assignment for the 179 patients in the pneumonia group was: FF 50 µg/VI 25 µg, n=48; FF 100 µg/VI 25 µg, n=51; FF 200 µg/VI 25 µg n=53; VI 25 µg, n=27. ^bOriginal treatment assignment for the 50 patients in the non-pneumonia group was: FF 50 µg/VI 25 µg, n=21; FF 100 µg/VI 25 µg, n=8; FF 200 µg/VI 25 µg n=11; VI 25 µg, n=10. ^cStudent's *t*-test.

Abbreviations: BMI, body mass index; CV, coefficient of variation; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FVC, forced vital capacity; ND, not determined; SE, standard error; VI, vilanterol.

$P=0.003$), and there was a trend for a lower baseline percent predicted post-bronchodilator FEV₁ (FEV₁%; 41.7% vs 45.2%; $P=0.096$). A higher proportion of patients in the pneumonia group had a history of pneumonia (36% vs 20%; $P=0.030$; OR: 2.28; Table S1). The baseline characteristics of the subset of 50 patients included in the non-pneumonia group appeared similar to the overall population of patients who did not develop pneumonia (Table S2).

A significantly higher proportion of patients in the pneumonia group than in the non-pneumonia group had a baseline CXR finding of elevated hemi-diaphragm (12% vs 2%, $P=0.033$; LR+: 6.15; LR–: 0.89; OR: 6.87; 95% CI: 0.90, 52.26); overall, this finding had the highest values for LR+ and diagnostic OR (Table 2). However, the opposite was evident for an alternative indirect sign of upper lobe volume loss (elevation of the right hilum), which was significantly less prevalent at baseline in the pneumonia group than in the

Table 2 Comparison of baseline CXR findings in patients with or without on-treatment pneumonia (independent blinded radiologist review)

CXR finding, n (%)	Pneumonia group (n=179)		Non-pneumonia group (n=50)		P-value ^b	LR+ ^c	LR– ^d	Diagnostic OR ^e (95% CI)
	Yes	No	Yes	No				
≥ 1 CXR finding ^a	179 (100)	0	50 (100)	0	–	–	–	–
Abnormal cardio/thoracic ratio measurement	53 (30) ^f	126 (70) ^g	12 (24) ^f	38 (76) ^g	0.437	1.23	0.93	1.33 (0.65, 2.75)
Atelectasis or other evidence of volume loss	31 (17)	148 (83)	9 (18)	41 (82)	0.911	0.96	1.01	0.95 (0.42, 2.16)
Basilar lines of COPD	11 (6)	168 (94)	5 (10)	45 (90)	0.344	0.61	1.04	0.59 (0.19, 1.78)
Blurring or loss of diaphragmatic shadow	21 (12)	158 (88)	5 (10)	45 (90)	0.733	1.17	0.98	1.20 (0.43, 3.35)
Calcified pleural plaque over the diaphragm or mid-chest pleural thickening ^h	5 (8)	60 (92)	0	15 (100)	0.578	2.67	0.95	2.82 (0.15, 53.76)
Elevation of hemi-diaphragm (indirect sign of volume loss [any lobe])	22 (12)	157 (88)	1 (2)	49 (98)	0.033	6.15	0.89	6.87 (0.90, 52.26)
Evidence of hiatal hernia ^h	2 (3)	63 (97)	2 (13)	13 (87)	0.158	0.23	1.12	0.21 (0.03, 1.60)
Focal/diffuse reticular-nodular or “ground glass” shadows	11 (6)	168 (94)	5 (10)	45 (90)	0.344	0.61	1.04	0.59 (0.19, 1.78)
Hyperinflated chest	172 (96)	7 (4)	47 (94)	3 (6)	0.458	1.02	0.65	1.57 (0.39, 6.30)
Indirect signs of upper lobe volume loss (elevation of the right hilum)	20 (11)	159 (89)	11 (22)	39 (78)	0.048	0.51	1.14	0.45 (0.20, 1.01)
Large cardiac silhouette	26 (15)	153 (85)	9 (18)	41 (82)	0.546	0.81	1.04	0.77 (0.34, 1.78)
Large/prominent pulmonary artery shadow	68 (38)	111 (62)	12 (24)	38 (76)	0.067	1.58	0.82	1.94 (0.95, 3.97)
Narrow cardiac silhouette	28 (16)	151 (84)	3 (6)	47 (94)	0.101	2.61	0.90	2.91 (0.85, 9.99)
Normal heart size in a hyperinflated chest (normal cardiac silhouette)	126 (70)	53 (30)	38 (76)	12 (24)	0.437	0.93	1.23	0.75 (0.36, 1.55)
Pleural thickening (any pleural change, apical, or basal can reflect sub pulmonary effusion or diaphragm shadow being indistinct)	71 (40)	108 (60)	20 (40)	30 (60)	0.966	0.99	1.01	0.99 (0.52, 1.87)
Pleural thickening at apices	18 (10)	161 (90)	6 (12)	44 (88)	0.692	0.84	1.02	0.82 (0.31, 2.19)
Pleural thickening at bases (including costophrenic angle blunting)	25 (14)	154 (86)	7 (14)	43 (86)	0.995	1.00	1.00	1.00 (0.40, 2.46)
Signs of bronchiectasis (not common few instances outside upper lobes)	7 (4)	172 (96)	2 (4)	48 (96)	1.000	0.98	1.00	0.98 (0.20, 4.86)
Signs of congestive heart failure in addition to large heart	6 (3)	173 (97)	1 (2)	49 (98)	1.000	1.68	0.99	1.70 (0.20, 14.45)
Thick tracheal-esophageal stripe on lateral view	7 (4)	172 (96)	0	50 (100)	0.352	4.25	0.97	4.39 (0.25, 78.22)
Vascular calcification, either coronary, carotid, or within the aortic shadow	74 (41)	105 (59)	18 (36)	32 (64)	0.496	1.15	0.92	1.25 (0.65, 2.40)

Notes: Statistically significant P -values ($P \leq 0.05$) are shown in bold. Gray shading indicates CXR findings with a diagnostic OR of > 2 . ^aIncludes patients with at least one CXR finding, excluding the finding of hyperinflated chest. ^bChi-square test or Fisher's exact test (the latter test was used if any values < 5). ^cLR+ defined as the ratio of the likelihood of observing the CXR finding in a patient who developed on-treatment pneumonia than in a patient who did not develop on-treatment pneumonia. ^dLR– defined as the ratio of the likelihood of not observing the CXR finding in a patient who developed on-treatment pneumonia than in a patient who did not develop on-treatment pneumonia. ^eDiagnostic OR defined as the ratio of the odds of being a true positive to the odds of being a false positive. An OR of > 1 indicates an association between the CXR finding and subsequent development of pneumonia, and < 1 indicates an association between the CXR finding and no subsequent development of pneumonia. ^fActual cardio/thoracic ratio measurement ratio was abnormal (< 0.5 or > 0.5). ^gActual cardio/thoracic ratio measurement was normal (0.5). ^hData missing for 114 patients in the pneumonia group and 35 patients in the non-pneumonia group; percentages are based on patients with available data.

Abbreviations: CXR, chest X-ray; LR+, positive likelihood ratio; LR–, negative likelihood ratio; OR, odds ratio.

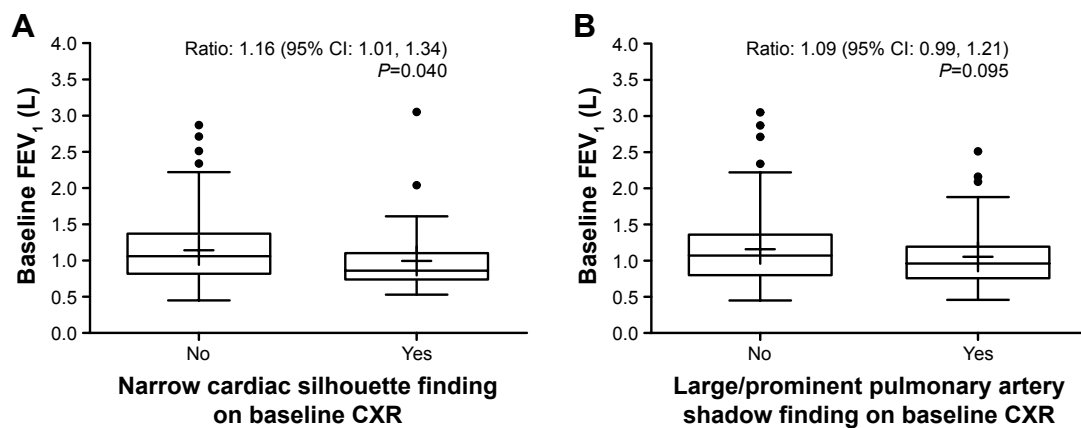


Figure 2 Relationship between baseline pre-bronchodilator FEV₁ and absence or presence of a narrow cardiac silhouette (A) or large/prominent pulmonary artery shadow (B) on baseline CXR.

Notes: Box-and-whisker plots are shown; each indicates the group mean, median, interquartile range, and minimum/maximum observations. *P*-value calculated from a Student's *t*-test of log-transformed FEV₁.

Abbreviations: CXR, chest X-ray; FEV₁, forced expiratory volume in 1 second.

non-pneumonia group (11% vs 22%, $P=0.048$; LR+: 0.51; LR-: 1.14; OR: 0.45 [95% CI: 0.20, 1.01]). Other baseline CXR findings with LR+ and diagnostic OR values >2 were a thick tracheal-esophageal stripe (4% vs 0%, $P=0.352$; OR: 4.39), narrow cardiac silhouette (16% vs 6%, $P=0.101$; OR: 2.91), and calcified pleural plaque over the diaphragm/mid-chest pleural thickening (8% vs 0%, $P=0.578$; OR: 2.82). In addition, the finding of large/prominent pulmonary artery shadow aligning the right mainstem bronchus was identified as having a diagnostic OR of ~ 2 (38% vs 24%, $P=0.067$; OR: 1.94).

We explored whether the presence of certain baseline CXR findings could be associated with subsequent pneumonia localization within the lung tissue (Table S3). We hypothesized that pneumonia would occur in the same hemithorax as did the findings of elevated hemi-diaphragm and calcified pleural plaque over the diaphragm/mid-chest pleural thickening; however, this ipsilateral relationship was found in only 10/20 and 2/9 cases, respectively. Furthermore, we examined whether the presence of a thick tracheal-esophageal stripe was associated with the presence of lower lobe pneumonia that reflected aspiration; this lower lobe relationship was observed in only 4/7 cases.

As the majority of patients had hyperinflation and the population had, on average, severe airflow obstruction, there was a rationale to try and relate lung function to the finding of narrow cardiac silhouette (indicative of significant obstruction with possible hyperinflation resulting in a shift in mediastinal structures). We observed a statistically significant higher mean pre-bronchodilator FEV₁ in patients without a narrow cardiac silhouette at baseline than in patients who

did have this finding (ratio: 1.16 [95% CI: 1.01, 1.34], $P=0.040$; Figure 2A). Furthermore, as the presence of a large/prominent pulmonary artery shadow may reflect pulmonary hypertension secondary to airflow obstruction and tissue hypoxia, it was also of interest to try and relate lung function to this CXR finding. We observed a trend toward a higher mean pre-bronchodilator FEV₁ in patients without a large/prominent pulmonary artery shadow at baseline than in patients with this finding (ratio: 1.09 [95% CI: 0.99, 1.21], $P=0.095$; Figure 2B).

Discussion

While previous studies in COPD have investigated the relationship between patient demographics/baseline disease characteristics and risk for pneumonia, the association between anatomical abnormalities of the lung as detected on routine CXRs and risk of developing pneumonia has not, to our knowledge, been studied.

This exploratory post hoc analysis of data from two previous randomized clinical trials in COPD¹⁵ sought to investigate whether baseline CXR findings could predict subsequent pneumonia development. Baseline characteristics significantly associated with development of pneumonia were lower BMI, lower post-bronchodilator FEV₁/FVC ratio, and prior history of pneumonia. The diagnostic OR for history of pneumonia was 2.28, with a CI that excluded unity. Furthermore, there was a trend for lower baseline post-bronchodilator FEV₁% in patients who developed pneumonia compared with those who did not. These findings are consistent with two previous studies of pneumonia risk in patients with COPD,^{5,6} suggesting that more severe airflow

obstruction at baseline is associated with an increased risk of developing pneumonia.

In this analysis, the presence on baseline CXR of an elevated hemi-diaphragm, thick tracheal-esophageal stripe, narrow cardiac silhouette, calcified pleural plaque/mid-chest pleural thickening, or large/prominent pulmonary artery shadow was associated with subsequent development of pneumonia; however, 95% CIs for the diagnostic ORs included unity in all cases. The LR+ was >2 for each of these findings (with the exception of large/prominent pulmonary artery shadow; LR+ of ~ 2), suggesting that an individual with pneumonia is more likely to test positive for these CXR findings than an individual without pneumonia; however, the LR- values were close to unity, meaning a negative finding would not be informative.

An elevated hemi-diaphragm, indicative mostly of lower lobe volume loss, supports the hypothesis that non-inflated lung tissue is prone to pneumonia. In contrast, upper lobe volume loss, reflected by elevation of the right hilum, appears to be associated with a lower risk of developing pneumonia.^{11,13} While there is no clear pathophysiological explanation for the latter phenomenon, it has been reported that lung volume reduction surgery improves the respiratory status of COPD patients with upper lobe emphysema;¹⁶ however, it is unknown whether lung volume reduction lowers the risk of developing pneumonia.

There was no difference in the distribution of abnormal or normal cardio/thoracic ratios between the pneumonia and non-pneumonia groups; however, the presence of a narrow cardiac silhouette did appear to predict for pneumonia risk. A narrow cardiac silhouette on CXR represents torsion of the mediastinal structures due to hyperinflation and suggests severe obstructive disease. Low FEV₁ has been previously reported to be a risk factor for pneumonia in patients with COPD.⁵ Accordingly, in the present analysis we observed a statistically significantly lower mean pre-bronchodilator FEV₁ at baseline in patients with a narrow cardiac silhouette as compared with patients without this finding.

The finding of a thick tracheal-esophageal stripe was only observed in the pneumonia group. One reported cause of this CXR finding is esophageal stricture secondary to GERD,¹⁷ a common comorbidity of COPD¹⁸ that increases patients' risk for aspiration-induced bronchitis and/or pneumonia.¹⁰ The presence of pleural shadows on the lateral wall of a posterior-anterior radiograph signifies a prior pneumonic process, for example, asbestosis-related disease, which could predispose to future infection.

Finally, the finding of an enlarged pulmonary artery shadow is indicative of pulmonary hypertension. If COPD-related

hypoxia were to be a cause of pulmonary hypertension, the enlarged pulmonary artery shadow, like the narrow cardiac silhouette, could be indicative of disease severity, which is itself a risk factor for pneumonia. Notably, we observed a trend for a lower mean pre-bronchodilator FEV₁ in patients with a large/prominent pulmonary artery shadow at baseline, compared with patients without this finding.

While CXR findings of elevated hemi-diaphragm, thick tracheal-esophageal stripe, or calcified pleural plaque/mid-chest pleural thickening were identified as potential markers for the development of pneumonia, additional exploratory analyses did not identify any clear relationship between these findings and subsequent pneumonia localization within the lung tissue.

There are several limitations to the present study that should be considered: 1) This was a post hoc retrospective analysis of data from two previously published trials, and our results require further exploration in a larger, prospectively designed study. 2) Due to the small sample size included in this analysis, there was no adjustment for baseline factors that may have been associated with development of pneumonia. ICS use has been associated with increased pneumonia risk in COPD,⁵ and it is worth noting that, in the included trials, three times as many patients were randomized to FF/VI than to VI. Of the 181 patients who developed on-treatment pneumonia, 85% were treated with an ICS-containing regimen compared with only 15% in the control arm.¹⁵ 3) Another limitation relates to the small number of patients randomly selected for inclusion in the non-pneumonia group and whether this subgroup is representative of the overall patient population that did not develop pneumonia; however, the two populations were found to be similar in terms of baseline demographics and lung function. Furthermore, while the control group did not develop pneumonia during the 1-year study period, they may not be truly representative of a patient population who never develop pneumonia (ie, they may not be true "negatives"). 4) The ratio of patients with and without pneumonia in the present analysis is not representative of the real-world scenario, and this impacts upon the ability to assess predictive measures such as positive predictive value, as prevalence is not reflective of the everyday clinical setting. 5) In this study design, there was no matching of time-at-risk between pneumonia cases and controls; an alternative approach would have been to identify a control at the time a case of pneumonia was found. 6) Consideration of the reliability of the association between baseline CXR findings and the timing of pneumonia development during the 1-year study period is also warranted. It is possible that the CXR findings detected at the baseline assessment may have differed to those

detected at the time of pneumonia diagnosis. 7) The CXR films reviewed in this analysis were derived from various imaging machines and study sites; consequently, there was no standardized radiographic magnification or kilovoltage exposure. Accordingly, we did not specify quantifying measures for CXR findings (eg, for height of diaphragm elevation, or size of pulmonary artery aligning the right mainstem bronchus) or assess CXR findings using a severity scale. Instead, the study relied on the subjective analysis of experienced radiologists to simulate “real-world” CXR review, and the practicality of reviewing many CXR images should be highlighted. 8) Finally, as a variety of baseline CXR findings were examined in this analysis, it is possible that some findings could have been observed by chance; therefore, this study should be viewed as hypothesis generating and not confirmatory.

The routine CXR has not commonly been used in the assessment of pneumonia risk. The extent of bronchiectatic and post-pneumonia alterations detected on CXR has been identified as a predictor of pneumonia in patients with cystic fibrosis;¹⁴ however, we are not aware of any similar studies in other chronic respiratory diseases. Understanding the increased risk for development of pneumonia based on a common clinical test could have an impact on the management of patients with COPD. If subsequent prospective studies confirm any of these anatomical abnormalities on CXR as being predictive of the likelihood of developing pneumonia, both patients and physicians could be especially vigilant for the signs and symptoms of incipient pneumonia, prompting earlier diagnostic evaluation of suspected cases. In addition, physicians may be encouraged to redouble their efforts to prevent pneumonia (eg, via methods such as vaccination, improving treatment adherence, home respiratory therapy, and employing prophylactic measures [such as avoiding ICS where possible]).

Conclusion

Our findings suggest that the presence of an elevated hemidiaphragm, thick tracheal-esophageal stripe, narrow cardiac silhouette, calcified pleural plaque/mid-chest pleural thickening, or large/prominent pulmonary artery shadow on routine CXR may be associated with the subsequent development of pneumonia in patients with COPD. These results warrant further exploration and confirmation in a prospectively designed study or a well-controlled retrospective cohort design in a larger patient population.

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Disclosure

DBR, SL, DVG, and CC: employment and stock ownership (GSK). SB: employment (GSK) at the time the analysis was conducted. HAA: employment and shareholder (Bristol-Myers Squibb). The current affiliation for HAA is Headquarters Medical, Immunoscience Marketed Products Development, Bristol-Myers Squibb, Princeton, NJ, USA. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Patients' medical history

Patients, n (%)	Pneumonia group (n=179)	Non-pneumonia group (n=50)
Any condition	138 (77)	31 (62)
Cardiac disorders		
Any condition	29 (16)	8 (16)
Arrhythmia	9 (5)	4 (8)
Congestive heart failure	3 (2)	1 (2)
Coronary artery disease	16 (9)	5 (10)
Myocardial infarction	10 (6)	3 (6)
Infections and infestations		
Any condition	65 (36)	10 (20)
Pneumonia	65 (36) ^a	10 (20) ^a
Metabolism and nutrition disorders		
Any condition	66 (37)	20 (40)
Diabetes mellitus	21 (12)	4 (8)
Hypercholesterolemia	47 (26)	17 (34)
Osteoporosis	15 (8)	5 (10)
Vascular disorders		
Any condition	81 (45)	19 (38)
Cerebrovascular accident	9 (5)	0
Hypertension	78 (44)	19 (38)
GERD ^b	28 (16)	11 (22)

Notes: ^aP=0.030 for between-group difference; odds ratio: 2.28 (95% confidence interval: 1.07, 4.86). ^bGERD as defined by receipt of GERD medications (proton-pump inhibitors, antacids, or other GERD therapy).

Abbreviation: GERD, gastroesophageal reflux disease.

Table S2 Demographics and baseline characteristics in the randomly selected non-pneumonia group and in all patients without on-treatment pneumonia

Patient characteristics	Non-pneumonia group (n=50)	All patients without on-treatment pneumonia (n=3,074)
Mean age (SD), years	63.8 (9.48)	63.6 (9.23)
Male/female, n (%)	26 (52)/24 (48)	1,762 (57)/1,312 (43)
Mean BMI (SD), kg/m ²	27.5 (5.26)	27.0 (5.87)
Ethnicity, n (%)		
Hispanic or Latino	13 (26)	556 (18%)
Other	37 (74)	2,468 (82%)
Mean post-bronchodilator FEV ₁ (SD), L ^a	1.25 (0.46)	1.29 (0.47)
Mean post-bronchodilator FEV ₁ /FVC ratio (SD), % ^a	47.6 (11.6)	45.7 (11.6)
Percent predicted post-bronchodilator FEV ₁ (SD), % ^a	45.2 (12.0)	45.7 (13.3)

Note: ^aData available for n=49 patients in the non-pneumonia group and n=3,045 patients in the entire group without on-treatment pneumonia.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

Table S3 Relationship between localization of CXR findings and subsequent pneumonia in lung tissue

Baseline CXR finding	Patients, n ^a	Relationship to localization of pneumonia (hemi-thorax)		
		Ipsilateral	Contralateral	Undetermined ^b
Elevated hemi-diaphragm	20	10	5	5
Calcified pleural plaque over the diaphragm/mid-chest pleural thickening	9	2	1	6
		Relationship to localization of pneumonia (lobe)		
		Lower	Upper	Undetermined ^b
Thick tracheal-esophageal stripe	7	4	2	1

Notes: ^aPatients with paired baseline and pneumonia CXRs (patients with pneumonia, available CXRs, and the relevant CXR finding). ^bNot possible to confirm clear change from baseline in infiltrates.

Abbreviation: CXR, chest X-ray.

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