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Original research article

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Relation between biomarkers and findings of low dose CT scans in hospitalized patients with AECOPD

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Sumary : 24% of the patients admitted with a COPD exacerbation had additional radiological abnormalities on their Low dose CT-thorax in spite of abscence of infiltrative changes on their chest X-ray. Patients with radiological abnormalities had significant higher levels of biomarkers(C-reactive protein, procalcitonin and serum amyloid A) however we were unable to reliably detect or exclude pneumonia with these biomarkers

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Abstract

Acute exacerbations of COPD (AECOPD) and community acquired pneumonia (CAP) often coexist. Although Chest X-rays may differentiate between both diagnoses, chest X-rays are known to underestimate the incidence of CAP in AECOPD. In this exploratory study, we prospectively investigated the incidence of infiltrative changes using low-dose CT-scan (LDCT). Additionally, we investigated whether clinical biomarkers of CAP differed between patients with and without infiltrative changes.

Methods: Patients with AECOPD in which pneumonia was excluded using chest X-ray underwent additional LDCT-thorax. The images were independently read by two radiologists, a third radiologist was consulted as adjudicator. C-reactive protein (CRP), procalcitonin (PCT), and serum Amyloid A (SAA) at admission were assessed.

Results: Of the 100 patients included, 24 patients had one or more radiographic abnormalities suggestive of pneumonia. The inter-observer agreement between two readers (Cohen's Kappa) was 0.562 (95%CI 0.371-0.752; p<0.001). Biomarkers were elevated in the group with radiological abnormalities compared to the group without abnormalities. Median CRP was 76 (IQR 21.5-148.0) mg/L compared to 20.5 (IQR 8.8-81.5) mg/L (p=0.018), median PCT was 0.09 (IQR 0.06-0.15) µg/L compared to 0.06 (IQR 0.04-0.08) ug/L (p=0.007) , median SAA was 95 (7-160) µg/ml compared to 16 (IQR 3-89) µg/ml (p=0.019). Sensitivity and specificity for all three biomarkers were moderate for detecting radiographic abnormalities by LDCT in this population. The area under the ROC curve was 0.66 (95% CI: 0.52-0.80) for CRP, 0.66 (95%CI: 0.53-0.80) for PCT, and 0.69 (95%CI: 0.57-0.81) for SAA.

Conclusion: LDCT can detect additional radiological abnormalities which may indicate acute-phase lung involvement in patients with AECOPD without infiltrate(s) on the chest X-ray. Despite C-reactive protein, procalcitonin and serum amyloid A being significantly higher in the group with radiological abnormalities on LDCT, they proved unable to reliably detect or exclude CAP. Further research is warranted.

Introduction:

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with short term and long term reductions in quality of life and lung function, as well as increased risk of death.[1-4] On average, a patient with COPD suffers from 1.5 exacerbations a year.[5] Moreover, AECOPD requiring hospital admission represents a significant prognostic factor for reduced survival across all stages of COPD severity.[6]

Patients with COPD have an increased risk of pneumonia, making it the most frequent infectious complication in COPD.[7] To complicate matters further, AECOPD and pneumonia are symptomatically alike, making it hard to diagnose pneumonia in COPD, based on clinical signs and symptoms alone.[8] Establishing a correct diagnosis is important for the guidance of antibiotic therapy. Misdiagnosing pneumonia could have great implications for patients, whereas over-diagnosing pneumonia leads to unnecessary exposure to antibiotics, which is a major driver of antimicrobial resistance.[9;10] Hence, clinicians have a keen interest in new biomarkers that together with clinical assessments may improve the diagnostic accuracy of pneumonia in patients with AECOPD. Potential biomarkers that are used in AECOPD to detect bacterial infection are C-reactive protein (CRP), Procalcitonin (PCT) and Serum Amyloid A (SAA).[11;12] Using these biomarkers as a diagnostic tool may increase the ability to detect clinically relevant bacterial infections at an early stage of the disease. Yet it is not known whether these biomarkers can differentiate between AECOPD and CAP. Therefore, current practice for detecting pneumonia in patients with AECOPD is the chest X-ray. One study showed that 20% of patients admitted to hospital with AECOPD had abnormalities on the chest X-ray consistent with pneumonia,[13] although this is probably an underestimation of the true incidence of pneumonia in patients with AECOPD; chest X-ray has limited sensitivity and specificity. Moreover, the interpretation of chest X-ray is often complicated by pre-existing cardiopulmonary diseases.[14;15] Chest CT scan however is able to outclass chest X-ray and is now considered the gold standard for diagnosing CAP.[16;17] However, CT delivers much higher radiation doses than do conventional diagnostic radiographs.[18] An alternative for conventional chest CT scan is the low-dose CT-scan (LDCT), that produces acceptable image quality with lower radiation exposure.

LDCT-scans have been shown to detect CAP if the chest radiograph does not reveal findings that explain the patient's clinical presentation.[19]

In this exploratory study, we prospectively aimed to investigate whether in patients with AECOPD admitted to hospital in whom pneumonia was excluded using chest X-ray, clinical biomarkers of CAP differed between patients with and without radiological abnormalities on LDCT We also investigated the interobserver variation in LDCT reading.

Material and methods.

One hundred consecutive patients were enrolled at the Northwest Clinics in Alkmaar between November 2011 and March 2014 as part of the CRP guided Antibiotic treatment of acute exacerbations of COPD admitted to Hospital study (CATCH study) (Clinical trial.gov NCT01232140)[20]. The local ethics boards approved the study protocol, and all patients provided written informed consent. The study population consisted of patients diagnosed with COPD stages I–IV as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [21]. Inclusion criteria dictate that patients had acute exacerbation as defined by GOLD requiring hospital admission according to GOLD guidelines[21], age above 40 years; and former or current smoking, with a minimum smoking history of 10 pack years. Exclusion criteria were: pre-treatment with oral corticosteroids exceeding a total dose of 210 mg prednisolone during the last 14 days preceding the presentation with AECOPD for hospitalization and pneumonia visualized on a chest X-ray. Immuno-compromised patients, and patients with active lung cancer and patients with pulmonary embolism were also excluded.

Procedures

Before informed consent was obtained, a chest X-ray was performed to rule out CAP. After informed consent was obtained, baseline blood samples were drawn and baseline variables were collected. LDCT was performed within 12 hours after informed consent was obtained using a standardized protocol. LDCT were performed on a CT Philips MX 8000 (16 slice) with the following settings: 90 kV en 25 mAs. CTDI 0.8 mGy and CT Somatom Definition Flash (128 slice Dual source CT) with the

following settings: 120 kV 20 mAs, CTDI 1.35 mGy. For both scanners acquisition and reconstruction was below 1 mm.

Image analysis

The images were independently read by two radiologists (EB and FJR). If there was a dispute between both radiologists considering the presence of an infiltrate, a third radiologist was consulted as adjudicator (PdJ). The readers had no knowledge of clinical or laboratory data, other than the age and sex of the patient. From a list of abnormalities (segmental, peribronchovascular or scattered ground-glass, reticular opacity or consolidation) at least one, or a combination of several abnormalities was used for the diagnosis of pneumonia assessed by LDCT scan.[22]

Biomarker measurements

Serum CRP was measured by nephelometry on a Beckman Synchron DxC 800 analyser (CRP latex Reagent, Beckman Coulter Inc; Fullerton, CA) CRP reference values: 0-5 mg/L. PCT was measured with Time-Resolved Amplified Cryptate Emission (TRACE) technology on a Kryptor Compact analyser (Thermofisher – B.R.A.H.M.S. GmbH Heningsdorf, Germany) with PCT sensitive KRYPTOR reagent (Thermofisher – B.R.A.H.M.S. GmbH Heningsdorf, Germany) PCT reference values: 0.00 – 0.10 µg/L. Serum amyloid A (SAA) was measured with an in-house sandwich ELISA. The ELISA test was calibrated against WHO standard 92/680; reference values were established as < 4.2 mg/L.[23] The test was performed at the Laboratory of Medicine of the University Medical Centre Groningen (UMCG, The Netherlands).

Microbiology

For all patients, sputum culture (if possible), nasopharyngeal swab for multiplex PCR for atypical and viral pathogens was obtained at admission. Additionally, paired serum samples were taken within 1 month for serology (Serion ELISA classic; Virion GmbH, Würzburg, Germany) for the detection of *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae, L. pneumophila* serogroup 1–7, influenza A and B virus, parainfluenza virus 1–3, respiratory syncytial virus, and adenovirus.

Statistical analysis

In this pilot study, our primary objective was to establish whether levels of CRP, PCT and SSA differed between patients with and without infiltrative changes on LDCT. As we were unaware of how many patients would have infiltrative changes on their LDCT, and how this would influence biomarker levels, we were not able to make a sample size calculation. Due to financial constraints, a convenience sample of 100 consecutive patients initially underwent a LDCT scan. Statistical analysis was performed with the SPSS Package Program (SPSS version 22.0). Data was presented as median (25^{th}–75^{th} quartile). In the comparison between groups, chi-square test and Mann-Whitney U test were used. The interobserver agreement was measured using Cohen's Kappa: κ<0.20 indicating poor agreement, κ of 0.21–0.40 fair, κ of 0.41–0.60 moderate, κ of 0.61–0.80 good, and κ of 0.81–1.00 indicates very good agreement between two observers. Receiver operating characteristics analysis was used to analyse the diagnostic accuracy of biomarkers. Overall statistical significance was set at a 2-tailed p value <0.05.

Results

A total of 592 patients presenting at our emergency department with AECOPD were screened for inclusion. One hundred patients (16.8%) were eligible and gave informed consent (figure 1). Twenty-four patients (24%) had radiological abnormalities compatible with acute-phase lung involvement detected by LDCT without abnormalities visible on chest X-ray (figure 2). Baseline characteristics of both groups are summarized in table 1 and did not show any significant differences between both groups except for oxygen saturation which was slightly lower in the group with radiological abnormalities.

Table 1 Baseline characteristics

	No radiological abnormalities present(n=76)	Radiological abnormalities present(n=24)	p value
Gender, male (%)	38(50)	12(50)	1.000
Age	71(62-77)	68(64-77)	0.707
FEV1, liters(IQR)[a]	1.13(0.82-1.46)	1.17(0.87-1.43)	0.710
FEV1, % pred(IQR)[a]	45(35-59)	42(34-61)	0.965
FVC, liters(IQR)a	2.76(2.05-3.63)	2.73(2.16-3.44)	0.803
FVC, %pred(IQR)[a]	82(74-99)	81(71-103)	0.954

FEV1/FVC, % (IQR)[a]	39.3(31.4-48.9)	38.5(30.6-47.0)	0.834
BMI, kg/m2 (IQR)	24.2(21.2-27.8)	23.6(21.8-27.8)	0.916
Current smoking, n(%)	22(28.9)	9(37.5)	0.430
Pack years, n(IQR)	43(24-53)	30(21-50)	0.207
Number of exacerbations last year, n(IQR)	1(1-2)	1(1-2)	0.311
Prior pneumonia, n(%)	12(15.8)	3(12.5)	0.694
History of heart failure , n(%)	4(5.3)	2(8.3)	0.581
Diabetes mellitus , n(%)	8(10.5)	1(4.2)	0.343
Pretreatment with antibiotics, n(%)	31(40.8)	10(41.7)	0.939
Pretreatment with systemic corticosteroids, n(%)	38(50.0	11 (48.8)	0.722
ICS usage, n(%)	18(23.7)	5(20.8)	0.722
Respiratory rate min (IQR)	20(16-24)	24(18-24)	0.151
Heart rate/ min (IQR)	89(78-102)	95(79-104)	0.412
Systolic blood pressure, mmHg (IQR)	148(131-162)	137(120-157)	0.108
Diastolic Blood pressure, mmHg (IQR)	86(71-93)	78(67-88)	0.252
Temperature C°(IQR)	37.2(36.7-37.7)	37.5(36.8-37.8)	0.440
Oxygen saturation, % (IQR)	94(92-96)	93(91-94)	0.041
CCQ at admittance, (IQR)	3.8(3.2-4.1)	3.8(3.1-4.3)	0.360
c-LRTI-VAS at admittance, (IQR)	23(19-27)	25(23-27)	0.816
Positive sputum culture at admittance, n(IQR)	25(32.9)	10(41.7)	0.432
CURB-65 score at admittance			
CURB65 0-1, n(%)	53(69.7)	17(70.8)	0.630
CURB65 2, n(%)	20(26.3)	5(20.8)	
CURB65 3-5, n(%)	3(3.9)	2(8.3)	

All data are represented as median (IQR) unless specified otherwise.
Definition of abbreviations: BMI: body mass index (kg/m2),
FEV1: forced expiratory volume 1 second, FVC: Forced Vital Capacity,
ICS: Inhaled corticosteroids, CCQ: Clinical COPD Questionnaire, c-LRTI-VAS: COPD lower respiratory tract infection visual anaologue score
[a]: Last recorded postbronchodilator value in a stable state before admission

The different types of radiological abnormalities are summarized in table 2.

Table 2 Types of radiological abnormalities	
	n=24
Consolidation, n(%)	15(62.5)
Tree in bud, n(%)	12(50.0)
Reticular changes, n(%)	9(37.5)
Bronchopathy, n(%)	7(29.2)

Results regarding sputum cultures are presented in table 3.

Table 3 Sputum culture

	No radiological abnormalities present(n=76)	Radiological abnormalities present(n=24)	p value
Representative sputum culture, n(%)a	25(32.9)	10(41.7)	0.432
Isolated pathogens from sputum			
	No infiltrate (n=25)	Infiltrate (n=10)	p value
H. influenzae, n(%)	10(40.0)	3(30.0)	0.580
S. pneumoniae, n(%)	6(24.0)	3(30.0)	0.714
H. parainfluenzae, n(%)	6(24.0)	2(20.0)	0.799
S. aureus, n(%)	3(12.0)	4(40.0)	0.061
Pseudomonas spp, n(%)	1(4.0)	2(20.0)	0.127
M. catharrhalis, n(%)	5(20)	0(0.0)	0.127
E.coli, n(%)	1(4.0)	2(20.0)	0.127
S. malthophilia, n(%)	1(4.0)	0(0.0)	0.521

a Sputum was representative according to the Bartlett criteria: sputum sample with >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field was defined as a sputum sample representative of the lower airways

Additional information regarding microbiological results in relation to the presence of radiological abnormalities can be found in table 1 and 2 in the supplemental materials.

Interobserver variation

The observed proportional agreement (P_0) in low-dose CT-scan judgment of observed abnormalities by radiologists A and B was 84.0%. The proportional agreement by chance (P_e) was 63.5%, resulting in a κ of 0.562 with a 95% confidence interval of 0.371 to 0.752 ($p<0.001$) reflecting moderate agreement. The proportional agreement in positive cases (P_{pos}, 69.6%) was lower than the proportional agreement in negative cases (P_{neg}, 88.3%). Fifty-two patients were scanned on a 128-detector row scanner and 48 on a 16-detector row scanner. On the 16-detector row scanner the agreement was 85.4% with a kappa of 0.543 (0.249-0.816). On the 128-detector row system the agreement was 82.7% with a kappa of 0.575 (0.333-0.816).

Biomarkers

All biomarkers were significantly higher in the group with radiological abnormalities on the LDCT compared to those without radiological abnormalities. CRP was 20.5 (IQR 8.8-81.5) mg/L in the group without radiological abnormalities compared to 76 (IQR 21.5-148.0) mg/L (p=0.018) in the group with abnormalities (figure 3a), whereas PCT was 0.06 (IQR 0.04-0.08) µg/L in the group without radiological abnormalities compared to 0.09 (IQR 0.06-0.15) µg/L (p=0.007) in the group with radiological abnormalities (Figure 3b). SAA was 16 (IQR 3-89) µg/ml in the group without radiological abnormalities compared to 95 (IQR 7-160) µg/ml (p=0.019) in the group with abnormalities (figure 3c). The area under the ROC curve for CRP was 0.66 (95% CI: 0.52-0.80), for PCT 0.66 (95%CI: 0.53-0.80) and for SAA 0.69 (95%CI: 0.57-0.81) (figure 4). The optimal cut-off value to identify radiological abnormalities was 43 mg/L for CRP, with a sensitivity of 0.70 and a specificity of 0.68. The optimal cut-off point for PCT to identify radiological abnormalities was 0.05 µg/L with a sensitivity of 0.78 and a specificity of 0.47. The optimal cut-off point for SAA to identify radiological abnormalities was 27 µg/ml with a sensitivity of 0.70 and a specificity of 0.65.

Discussion

In this exploratory study we show that 24% of the patients with AECOPD admitted to hospital without evidence of pneumonia on chest X-ray had additional radiological abnormalities on LDCT. In patients with radiological abnormalities on LDCT, the levels of CRP, PCT, and SAA were higher than in those without LDCT abnormalities. However, we were unable to reliably exclude or confirm the diagnosis of CAP using these biomarkers.

The incidence of infiltrative changes in AECOPD not detected by chest X-ray was considerably higher than in an earlier study, among 47 patients suspected to have CAP; while confirming CAP in 18 patients, in 8 more patients, CAP could be detected with high-resolution (HR)CT.[22] The higher number of infiltrates found in this study may be explained by a difference in baseline population. As our study consisted of hospitalized patients with AECOPD while the aforementioned study consisted of patients of the general population with fever and cough.

The κ value of agreement between both radiologists was moderate (κ 0.562) and lower compared to some previous studies.[22] This can most likely be explained by a combination of small infiltrates that are more difficult to diagnose and the low-dose CT technique instead of high-resolution CT.[22]

CRP, SAA and PCT were elevated in the group with consolidations. However they were considerably lower compared to other studies in patients with radiographic confirmed pneumonia.[24;25] The biomarkers reported in the group without radiological abnormalities were comparable to an earlier study in patients with AECOPD.[11] CRP, SAA, and PCT showed poor sensitivity and specificity for the prediction of radiological abnormalities on LDCT. In part this might be due to the fact that all biomarkers in this study are used in the detection of bacterial infection, whereas these radiological abnormalities can also be caused by viral infections.[11;26] This might subsequently lead to a lower level of these biomarkers compared to bacterial infection.[27;28] To complicate matters further, definite diagnosis of viral or bacterial origin cannot be achieved using imaging features alone. However, recognition of viral pneumonia patterns may help in differentiation between viral pathogens and bacterial pathogens, with subsequent reduction of unnecessary use of antibiotics.[29]

A potential strength of this study is that all data were collected prospectively, thereby not resulting in selection bias. Another strength is the fact that radiologists were blinded for clinical data except for age and gender, so this could not have influenced their judgement. A potential limitation is design of our study, as patients were allowed to have a 12-h time gap between the initial chest X-ray and the LDCT. Infiltrative changes may progress over time, that may have led to progression or emergence of new radiological abnormalities. The second limitation is the prescription of antibiotics or systemic corticosteroids prior to inclusion. We cannot exclude that these pre-treated patients may have altered biomarker performance, or that remnants of infiltrates invisible to chest X-ray still can be detected on CT. The third potential limitation is the fact that CT cannot discriminate between viral and bacterial CAP, as only invasive local microbiological sampling would have provided this diagnostic precision.[29] As we did not gather these data, results regarding the differences between biomarker levels and LDCT findings should be interpreted with caution. Fourth weakness is that this is an explorative study and not powered to detect differences in biomarkers. Finally, our study was performed between 2011 and 2014.

CT detector and reconstruction technology is continuously evolving. Iterative reconstruction lowered noise (and dose), but altered the lung appearance in some instances. With the most recent CT advances resolution can be further improved. It may be that the detection of pneumonia will even further improve and that we missed some very subtle cases.

AECOPD and pneumonia have considerable symptomatic overlap, and ruling out CAP using a chest X-ray is often difficult. We have shown that using LDCT, it is possible to detect additional radiological abnormalities in patients with AECOPD. However the question remains what the outcome means for the individual patient as the abnormalities found are divers and do often not reflect a specific aetiology. Biomarkers are increased in patients with infiltrative changes on their LDCT. Yet CRP, PCT, nor SAA carried sufficient weight to confirm or exclude the diagnosis of CAP in this specific population. Therefore, further research is necessary to determine whether the presence of additional infiltrative changes on LDCT represents a categorically different disease process or rather a spectrum of infection, especially in the light of the similarity between clinical characteristics and microbiology.

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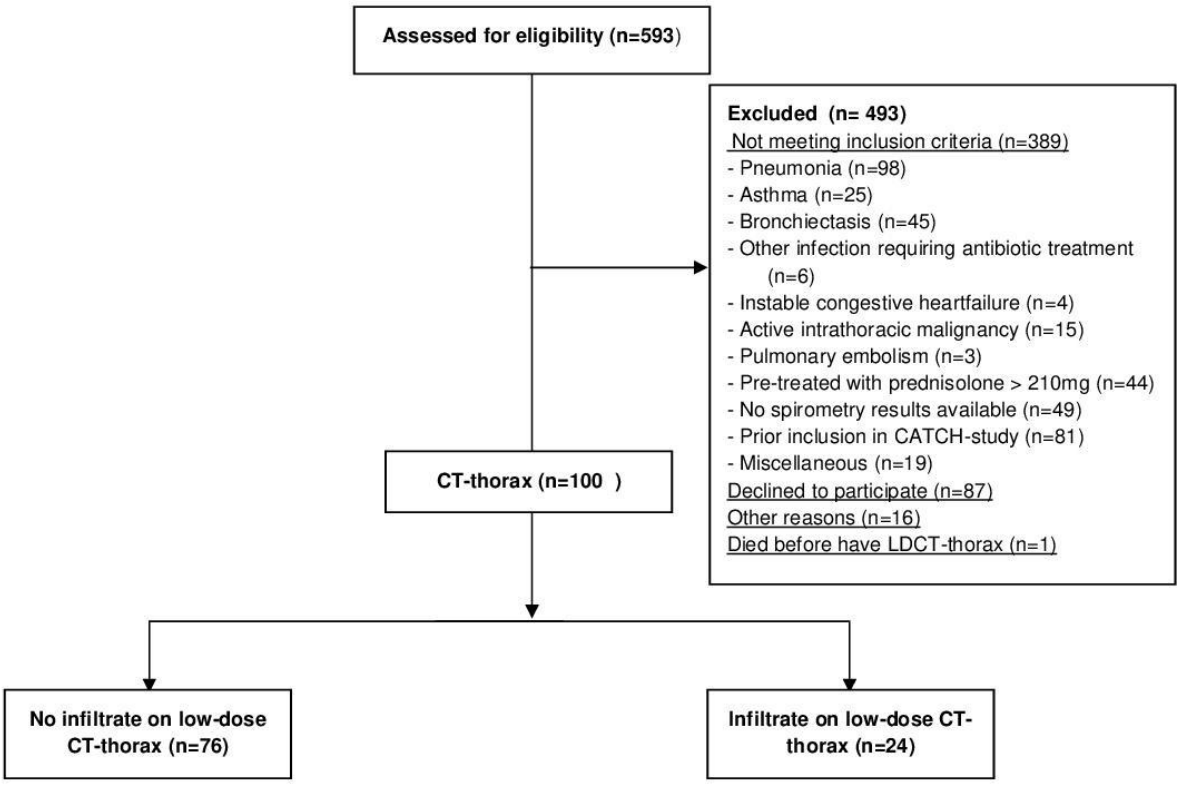
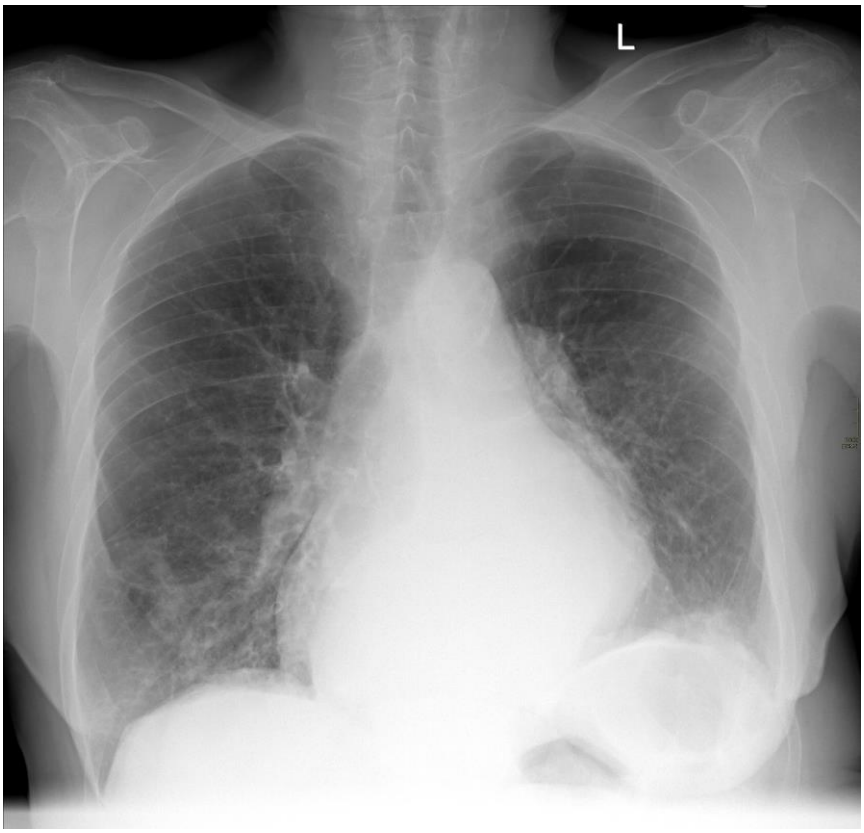


Figure 1 trial profile

Figure 2



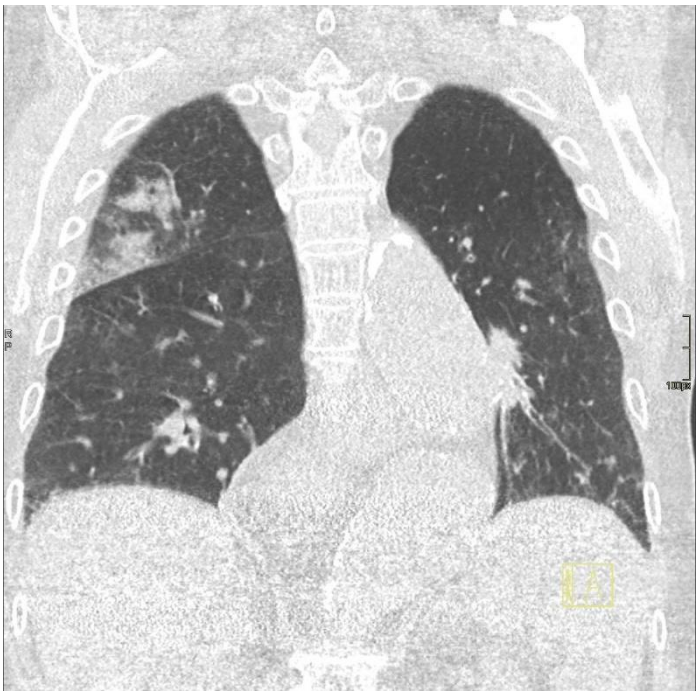


Figure 3

Figure 3A. CRP level in patients with and without radiological abnormalities

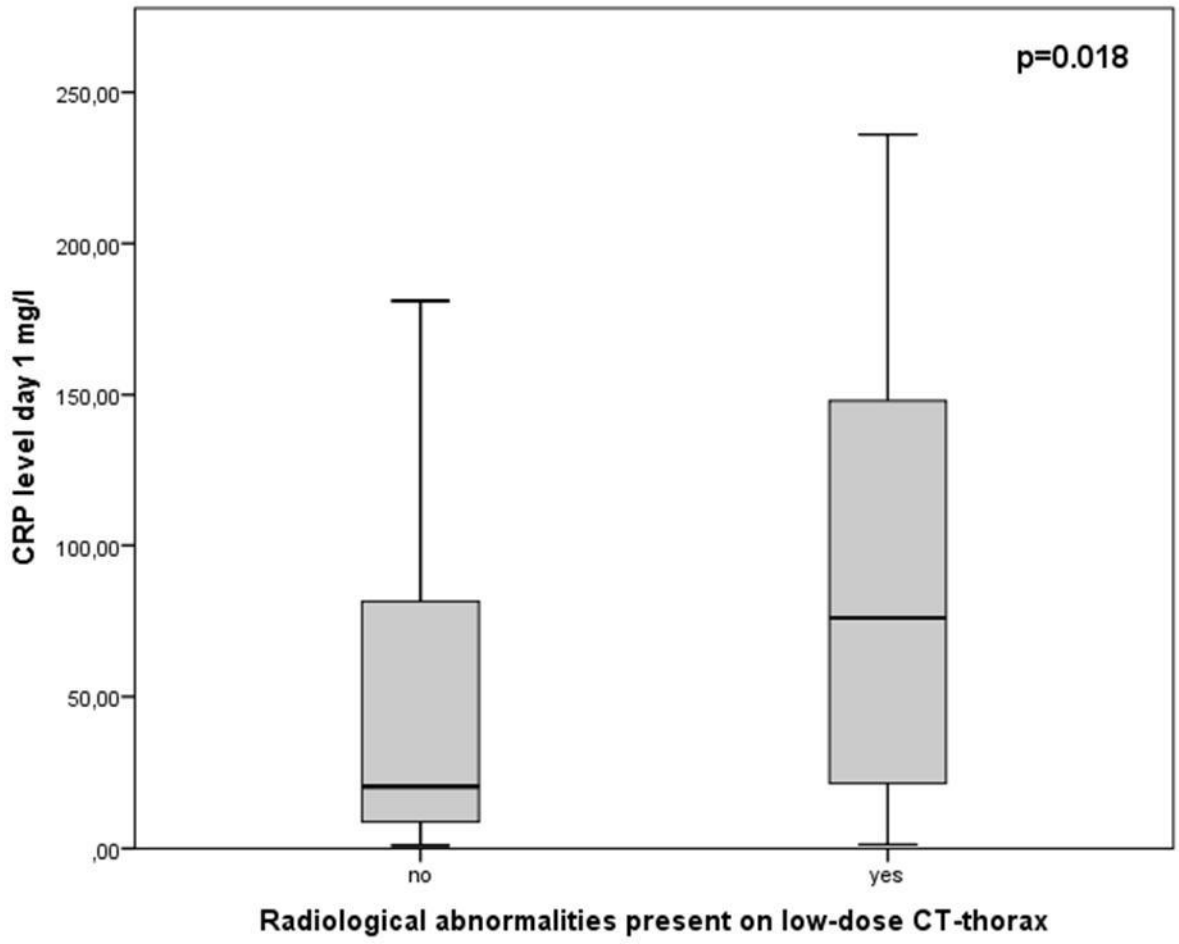


Figure 3B. PCT level in patients with and without radiological abnormalities

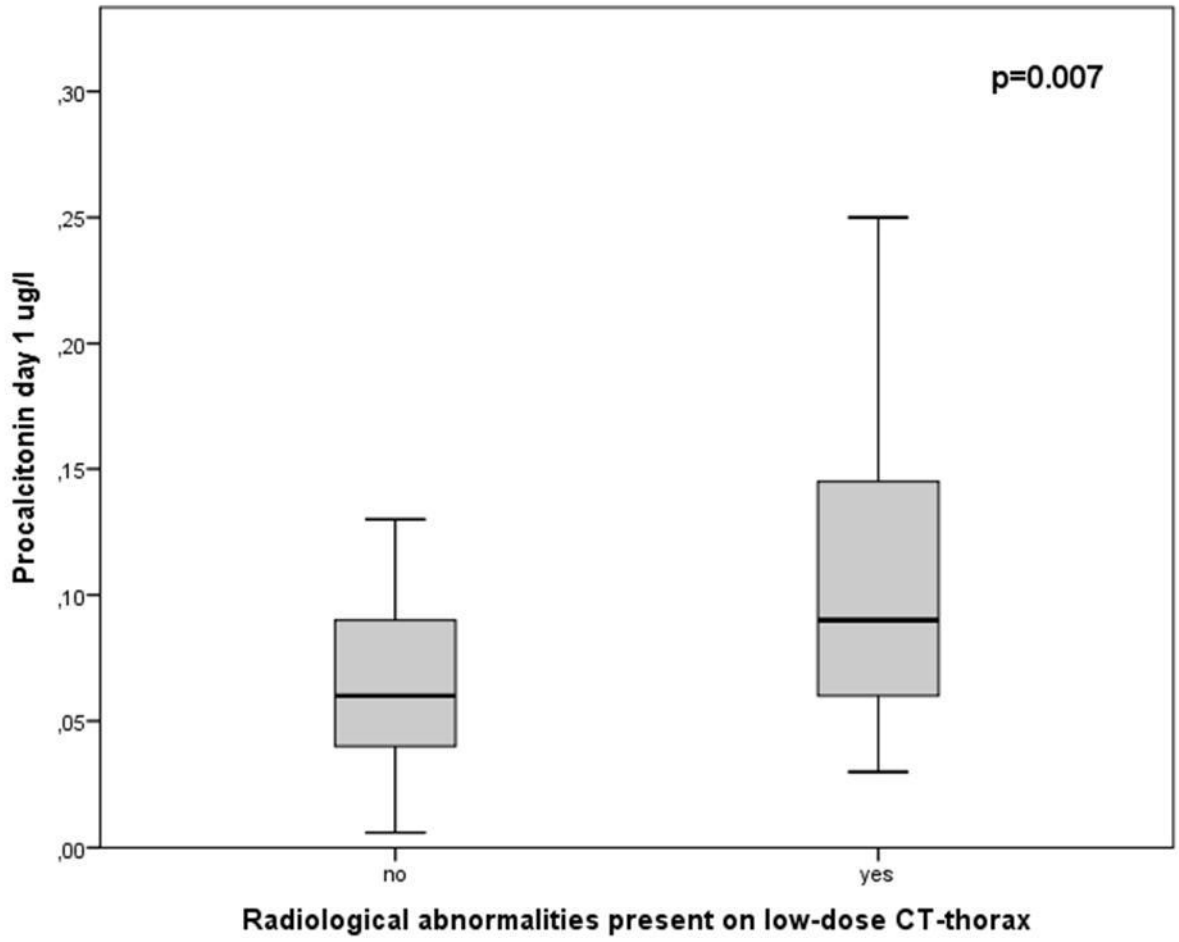


Figure 3C SAA level in patients with and without radiological abnormalities

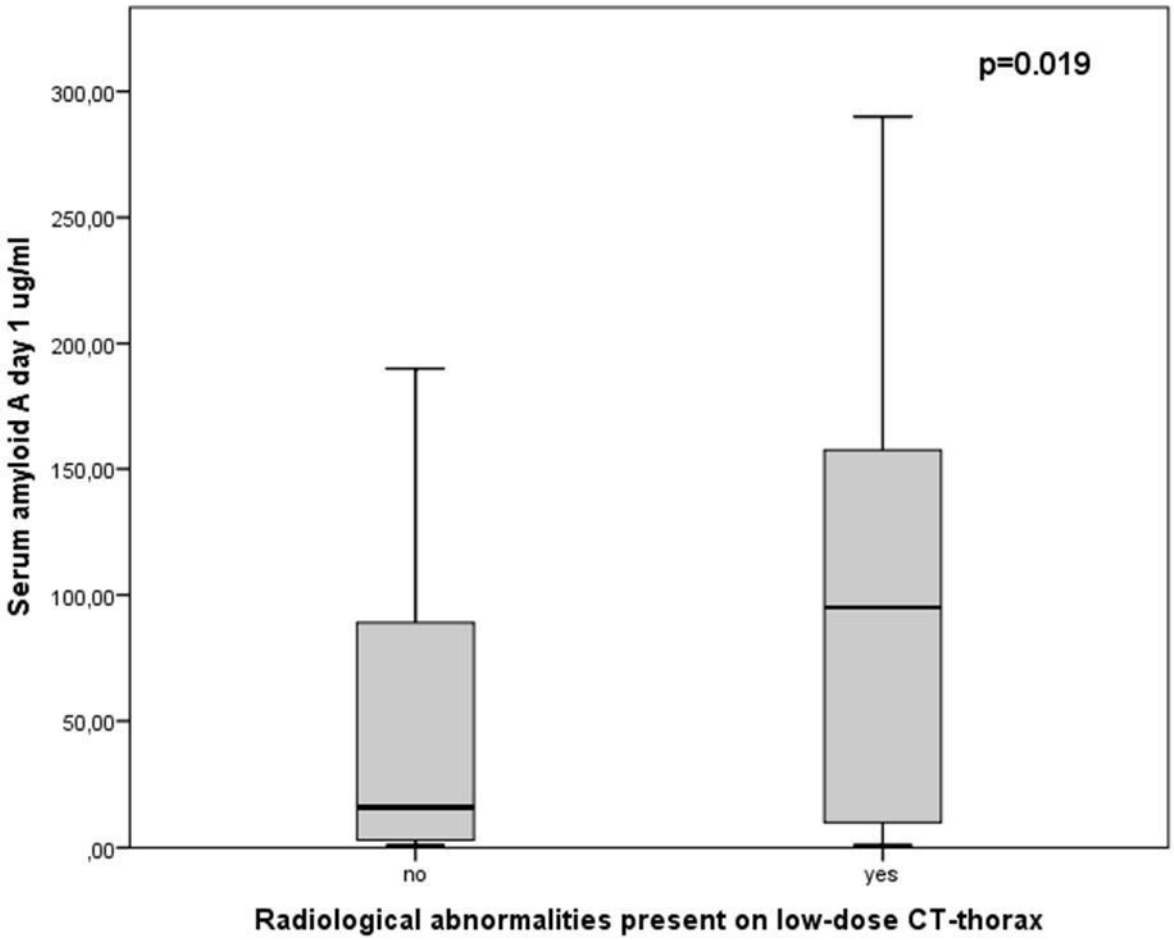


Table 1 online data supplement microbiological results in relation to the presence of radiological abnormalities on LDCT				
	Number of available samples	Radiological abnormalities present(n=24)	No radiological abnormalities present (n=76)	p-vallue
Positive Sputum culture	35	10(41.7)	25(32.9)	0.432
Positive Virological serology	78	3(17.6)	7(11.5)	0.501
Positive PCR results	44	3(33.3)	8(22.9)	0.517

Table 2 online data supplement type of radiological abnormality in relation to pathogen				
	consolidation (n=15)	tree in bud(n=12)	Reticular patern(n=9)	Bronchopathy(n=7)
Sputumculture				
H. influenzae	3	0	2	1
S. pneumoniae	1	1	3	1
S. aureus	2	3	2	3
P.aeruginosa	2	2	0	0
E. coli	1	1	1	1
H. parainfluenzae	2	2	0	0
Airway serology				
Influenza A virus	1	1	1	0
RS virus	1	2	0	0
PCR results				
Rhinovirus	1	0	0	0
Influenza A virus	0	1	0	0
RSV Virus A	0	1	0	0