ERJ Express. Published on April 12, 2018 as doi: 10.1183/13993003.02375-2017

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Prendki V, Scheffler M, Huttner B, *et al*. Low-dose CT for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.02375-2017).

Low-dose CT for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study

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Short running-title: PneumO-LD-CT

Keywords: chest X-Ray, computed tomography, lung infection, pneumonia/diagnosis, aged, net reclassification improvement

Abstract

The diagnosis of pneumonia is challenging. Our objective was to assess whether a low-dose computed tomography (LDCT) modified the probability of diagnosing pneumonia in elderly patients.

We prospectively included patients aged over 65 years, with a suspicion of pneumonia treated with antimicrobial therapy. All patients had a chest radiograph and LDCT within 72 h of inclusion. The treating clinician assessed the probability of pneumonia before and after the LDCT by using a Likert scale. An adjudication committee retrospectively rated the probability of pneumonia and was considered as reference for diagnosis. The main outcome was the difference in the clinician's pneumonia probability estimates before and after LDCT and the

proportion of modified diagnoses which matched the reference diagnosis (net reclassification improvement (NRI)).

200 patients with a median age of 84 years were included. After LDCT, the estimated probability of pneumonia changed in 90 (45%) patients: 60 (30%) were downgraded, 30 (15%) upgraded. The NRI was 8% (NRI event -6% + NRI non event 14%).

LDCT modified the estimated probability of pneumonia in a substantial proportion of patients. It mostly helped to exclude a diagnosis of pneumonia and hence to reduce unnecessary antimicrobial therapy.

Introduction

Pneumonia is highly ranked amongst causes of hospitalisation in the elderly and is the leading cause of death from infection in patients aged 65 years or older [1]. The incidence of community-acquired pneumonia (CAP) increases with age, from 2.81 (65–69 years old) to 21.81 (85–89 years old) episodes/1000 person-years [2]. In a US cohort of 6205 patients with a mean age of 67 years, 30-day mortality from CAP was 8.2% for all patients and 16.1% in the group of patients aged over 80 [3].

According to international recommendations, the standard criteria for the diagnosis of pneumonia are the presence of acute respiratory symptoms and/or fever associated with newly identified or modified infiltrates on a chest x-ray (CXR) [4 5]. However, particularly in the elderly, clinical symptoms and signs of pneumonia are often atypical and CXR abnormalities may be absent, delayed or non-specific [6-10]. Both performing and interpreting high-quality CXRs in this population has multiple limitations [11]. Furthermore, there is significant inter-observer variability in the interpretation of CXRs, even among experienced radiologists [12-14]. Correctly diagnosing pneumonia is essential to avoid both under-diagnosis, with the risk that late treatment initiation might harm the patient, and over-diagnosis, leading to over-consumption of antibiotics [15]. Previous data have shown the superiority of LDCT over CXR for the diagnosis of pneumonia in different populations [11 16-18]. The potential impact of a strategy to systematically carry out thoracic CT scans for diagnosing pneumonia in elderly patients merits further analysis. We aimed to analyse how low-dose CT (LDCT) chest scanning modifies the probability of a diagnosis of pneumonia in elderly patients.

Material and methods

Ethics statement

The Geneva institutional review board approved the study protocol (CER 14-250), which was also registered in www.clinicaltrials.gov (NCT02467192). All enrolled patients provided

written informed consent before inclusion and consent from next of kin was obtained for decisionally impaired patients.

Setting

This study was conducted in the Department of Internal Medicine, Rehabilitation and Geriatrics at Geneva University Hospitals, in Switzerland, a 1,800-bed tertiary care institution serving a population of about 500,000 inhabitants.

Study population

Between 1 May 2015 and 30 April 2016, we enrolled consecutive hospitalised patients aged 65 years old or more, with a suspicion of CAP or hospital-acquired pneumonia, and being treated with antimicrobial therapy (AT) for that indication. A clinical suspicion of pneumonia required the presence of at least one respiratory symptom (new or increasing cough, purulent sputum, pleuritic chest pain, new or increasing dyspnoea, respiratory rate >20/min, focal auscultatory findings or oxygen saturation <90% on room air) and at least one symptom or laboratory finding compatible with an infection (temperature >38.0°C or <35.0°C, C-reactive protein (CRP) >10 mg/L, leukocyte count >10 G/L with >85% neutrophils or band forms) [4]. A CXR image suggestive of pneumonia was not necessary for inclusion. Patients who had been treated for pneumonia during the previous six months, who had already undergone a CT scan during the present episode or needed a contrast-enhanced CT, who had been admitted to the intensive care unit (ICU), or who had already been treated with AT for more than 48 h before inclusion were excluded as well as decisionally impaired patients for whom the family could not provide consent. Community- and nursing home-acquired pneumonia were defined according to where patients lived; hospital-acquired pneumonia was defined as pneumonia developing two or more days after hospitalisation.

Patient management and data collection

Patients were managed according to local guidelines and screened by the study nurse. Both the choice and duration of AT were left to the discretion of the treating clinician, with the help

of institutional recommendations (appendix). Demographic data, comorbidities, vital signs, clinical findings, severity scores and the results of standard laboratory tests, including CRP, procalcitonin (PCT), polymerase chain reaction (PCR) for respiratory viruses on naso-pharyngeal swabs, blood, sputum and urine cultures, and urinary antigens were prospectively recorded at baseline.

Radiological data

CXRs were obtained for all patients, preferably while standing, and with postero-anterior and lateral incidence if possible. The clinician assessed the probability of pneumonia by integrating the results of the clinical examination, biological data and the results of the CXR, and then graded the probability of pneumonia on a five-level Likert scale (excluded, low, intermediate, high, certain). A LDCT scan, without administration of intra-venous contrast, was performed as soon as possible after the first Likert scale estimate, ideally within 24h of inclusion in the study, but no later than 72h. A new CXR was performed if the delay between the first CXR and the CT scan was more than 12 h. LDCT images were interpreted by the attending radiologist, who was informed of the clinical suspicion of pneumonia but had no other medical information and was not directly involved in the study. In addition to the usual description of the image, the radiologist graded the probability of pneumonia on the previously mentioned five-level Likert scale. The clinician then made a new evaluation of the probability of pneumonia by incorporating the results of the LDCT and the radiologist's interpretation. Finally, the clinician decided whether to continue or withdraw the AT. The investigators had no influence over decisions regarding AT.

Adjudication committee

After completion of the study, an adjudication committee (appendix), blinded to the results of the LDCT scan, retrospectively rated the probability of pneumonia according to patient records and based on international guidelines for diagnosis of pneumonia [4 5]. Their final decision was considered as the reference diagnosis.

Outcomes

The study's primary endpoint was the proportion of patients whose probability of pneumonia changed (upgraded or downgraded) before and after LDCT and the proportion of modified diagnoses which matched the reference diagnosis. Secondary endpoints were: the test characteristics (sensitivity, specificity, likelihood ratios, positive and negative predictive values and Receiver Operating Characteristic curve (ROC curve)) of LDCT in comparison to the reference diagnosis; the rate of agreement between the adjudication committee's experts; the proportion of patients for whom AT prescribed for pneumonia was discontinued after the LDCT, for all the patients and for those with a low post-LDCT probability, and the prevalence of ancillary findings on LDTC.

Statistical analyses

Baseline characteristics were described using means (standard deviations, SD), medians (inter-quartile ranges, IQR) and proportions (95% confidence intervals, CI) as appropriate. The estimated probabilities of pneumonia before and after the LDCT were compared, and the proportion of modified diagnoses (95% CI) was calculated. For clarifying the comparison of pre-LDCT and post-LDCT probability, high and certain probabilities as well as low and excluded probabilities were regrouped, leading to a three-level Likert scale. To assess whether LDCT helped the clinicians to properly reclassify patients in agreement with the adjudication committee's reference diagnoses, we calculated the net reclassification improvement (NRI). The absolute NRI calculates the absolute number of patients correctly reclassified: net reclassification of patients with pneumonia (NRI event) plus net reclassification of patients without pneumonia according to the adjudication committee (NRI non event) on the total number of patients [19 20]. Patients with intermediate or high probability of pneumonia according to the adjudication committee were considered as having pneumonia, and patients with low probability considered as not having pneumonia.

We compared LDCT's parameters for diagnosing pneumonia according to the radiologist and then for diagnosing pneumonia according to the clinician with the results of LDCT, against those of the reference diagnosis. We calculated a first ROC curve of the true-positive rate (sensitivity) against the false-positive rate (1 minus specificity) of the LDCT, compared to the reference diagnosis (with pneumonia if intermediate or high probability, or without if low probability, Figure 2) and a second one showing the accuracy of the post-LDCT probability against the reference diagnosis (Figure 3, appendix).

The rate of agreement between the adjudication committee members was calculated (appendix).

Analyses were performed using the R statistical software package, version 3.1.1 (www.cran.r-project.org).

Sample size

In a previous study [21], a CT scan modified the diagnostic classification of CAP in 59% of cases (95% CI, 53.2–64.0), with an upgraded probability of diagnosis in 19%. Demonstrating an improvement in the pneumonia detection rate by using CT would require 46 patients (p=0.05, power 90%). Considering a true incidence of pneumonia of 45% among patients hospitalised for pneumonia, according to the adjudication committee's reference diagnosis, we calculated that at least 100 patients would be needed to allow the estimation of any changes in a diagnosis of pneumonia. Moreover, the present study took place over a period of one year in order to avoid any seasonal bias and thus allow for the inclusion of a broad range of pneumonia, including those seen during winter flu epidemics.

Results

Patients' characteristics

Of 899 patients screened, 200 were included (Figure 1). Characteristics are provided in Tables 1 and 2. The median delay of LDCT was 2.2 hours after inclusion.

The initial probability of pneumonia was high in 56.5% (113), intermediate in 35% (70) and low in 8.5% (17) patients. After the LDCT scan, those probabilities became high in 57% (114), intermediate in 14.5% (29) and low in 28.5% (57) patients. The LDCT results changed the probability of pneumonia in 90 patients (45%). The probability was upgraded in 15% (30) of patients and downgraded in 30% (60) (Table 3). More than 80% of patients with intermediate pre-LDCT probability had their probability changed after LDCT. The changes in clinician's probability subsequently matched the reference diagnoses in 67.8% of modifications (61/90) and in 30.5% of all patients (61/200). The absolute number of patients correctly reclassified according to the diagnosis of adjudication committee is –12 patients among those with pneumonia, and +28 among those without pneumonia. Overall, the absolute number of patients correctly reclassified is thus +16 patients, corresponding to 8.0% of all patients in our sample (Table 4).

Comparing the probability of a pulmonary infiltrate on the LDCT interpreted by a radiologist and the diagnostic probability of pneumonia by the adjudication committee, we identified 113 true-positive, 44 true-negative, 13 false-positive and 30 false-negative cases. This provided the following measures of accuracy: sensitivity (0.79), specificity (0.77), positive predictive value (0.90), negative predictive value (0.59), positive likelihood ratio (3.46), negative likelihood ratio (0.27) and AUC=0.79 (95%CI: 0.73-0.86) (Figure 2). When using the adjudication committee as reference, the diagnostic performance of the clinician with access to the LDCT, expressed as AUC of a ROC curve, was 0.847 [95% CI: 0.7907-0.9032] (Figure 3 in appendix). Among the 30 false negative cases (low probability of diagnosis of pneumonia on LDCT and intermediate or high probability according to the members of the adjudication committee), 23 cases (77%) were of intermediate probability according to the adjudication committee and 7 were judged to have a high probability of pneumonia.

The initial agreement rate between the experts of the adjudication committee for the probability of pneumonia was 31.5% using a three-level Likert scale.

The prevalence of findings other than pneumonia was 38%. Pulmonary nodules requiring further examination were present in 19 (9.5%) cases. Other identified findings are provided in Table 5. The LDCT scan results led the clinician to withdraw AT in 8.5% of all the patients and 30% of the patients with a low post-LDCT probability, without any intervention from the study team. Of note, the presence of an infectious differential diagnosis justified the continuation of AT in 29 (51%) patients with a low post-LDCT probability (Table 6, appendix).

Discussion

To the best of our knowledge, this is the largest prospective study assessing the utility of low-dose computed tomography (LDCT) chest scans in a cohort of elderly people with suspected pneumonia, to date. LDCT results changed the probability of a diagnosis of pneumonia in a high proportion of patients (45%), upgrading the probability in 15% and downgrading it in 30%. These changes matched the reference diagnoses in 30.5% of all patients. The absolute net reclassification index was 8% and NRI non event was superior to NRI event, meaning that LDCT mostly helped to exclude a diagnosis of pneumonia. We found fair positive-likelihood and negative-likelihood ratios for CT and a low agreement rate for the probability of pneumonia among the members of the adjudication committee. LDCT allowed supplementary findings in 38% and led the clinician to withdraw antibiotics in 8.5% of all patients and in 30% of the patients with a low post-LDCT probability.

A recent prospective study of CT's impact on the diagnosis of CAP in 319 adults (mean age, 65 years old) consulting in the emergency department reported similar results. In this study, chest CT led to a change of diagnosis in 59% of cases: probability of pneumonia was lowered in 40% of cases and raised in 19% [21]. The NRI reported in Claessens' study was 18.8% (NRI event -0.6% and NRI non event 19.4%). Interestingly, both in our study and in the study by Claessens et al, correct reclassification was mainly observed in patients not having pneumonia according to the reference diagnosis. This means that LDCTs potential benefit would mainly be to reduce the overdiagnosis of pneumonia. Pneumonia overdiagnosis is an important issue in terms of costs and inappropriate antibiotic use leading

to potential complications and selection of resistant strains. Some studies have reported that less than half of patients treated for pneumonia in US hospitals satisfied diagnostic criteria for pneumonia [15]. Moreover, CXR lacks sensitivity for the diagnostic of pneumonia, and LDCT may allow detection of pulmonary infiltrates not diagnosed on the CXR, especially among elderly. In a previous study, CXRs and full-dose CT scans were performed on 58 bedridden patients with a mean age of 84 years and an intermediate or high probability of pneumonia. CT scans allowed a positive diagnosis of pneumonia in 53%, compared with 21% with a CXR. Of the 11 patients with a normal CXR, 6 (55%) had CT scans showing bilateral infiltrates [11]. Nevertheless, this study did not include comparison with a reference diagnosis. In our study, 8 of the 17 patients whom clinicians had initially considered as having a low probability of pneumonia had an intermediate or high probability according to the reference diagnosis. Similarly, Claessens et al. found infiltrates on the CT scans of 40 out of 120 patients considered as having a low probability of pneumonia based on CXR. Unfortunately, we were not able to evaluate the benefit of LDCT in terms of sensitivity improvement since patients judged not to have pneumonia based on the initial clinical and radiological assessment (hence potential false negative of patients in the initial evaluation that could have been identified by a LDCT) were not included in the study.

The overall performance of LDCT was higher in the study by Claessens et al than in the present study. For example, reclassification matched Claessens et al.'s reference diagnosis in 80% of cases, compared to 67.5% in the present study. This discrepancy may be explained by the use of different reference diagnosis definitions. In the Claessens study the adjudication committee had access to the LDCT scan results, which may have led to an overestimation of the LDCT diagnostic performance due to the incorporation bias of using the LDCT for the reference diagnosis. We instead chose to blind our adjudication committee to the LDCT results in order to remain conservative in the evaluation of LDCT diagnostic improvement.

The present study only found fair positive-likelihood and negative-likelihood ratios for CT, but these evaluations were set against an arguable reference diagnosis. Some patients without infiltrate on the LDCT and considered as LDCT false negatives may rather be false positives of our reference diagnosis (diagnosis of pneumonia established by the expert committee blinded to the CT results). Of note, five of them had heart failure, a diagnosis that can confound the interpretation of CXR. The rate of agreement for the diagnosis of pneumonia among experienced clinicians was low, although they had access to all the clinical information, including patient outcomes. This highlights the difficulties in making unambiguous diagnoses based on international recommendations: there is an even greater lack of sensitivity and specificity in the clinical and radiological examinations of elderly patients [8 11 22].

The diagnosis of pneumonia in current clinical practice is likely flawed by both over- and under-diagnosis. Under-diagnosis exposes patients to delays in the initiation of antibiotic treatment, which might worsen their prognosis. On the other hand, in addition to the failure to identify the real cause of a patient's symptoms, over-diagnosis can lead to excessive use of antimicrobials [23]. In our study, the clinicians stopped AT in 8.5% of patients after the result of LDCT, with no intervention from the study team. This should be compared with 28% of patients diagnosed with a low post CT probability of pneumonia. Failure to withdraw antibiotics, even when the probability of pneumonia is judged to be low, may be the result of the clinicians' lack of confidence in the diagnosis, overestimation of the benefits of antibiotics in respiratory tract infections other than pneumonia, or underestimation of the adverse consequences of their overuse. Moreover, patients may present with an other source of infection requiring AT, as was the case for 29 (14.5%) patients in our study.

Our study demonstrates the feasibility of using LDCT scanning for elderly people hospitalised in our institution while only one third of them received standing and profile CXRs. LDCT scans took 10 minutes to perform, were well-tolerated, with a mean radiation exposure was 1.5 +/- 0.47 mSv. This can be compared to a mean exposure of 0.05 +/- 0.03 mSv for the

conventional CXR, to Switzerland's natural background radiation level of 4mSv/year and 7 mSv for a full-dose CT scan [24]**.** However, CT scanners are not available everywhere and scans are more expensive than CXRs. In Switzerland, the cost of a chest CT is about three times that of a chest X-ray, but the total costs and ratio of these exams vary widely from one country to another.

Moreover, additional radiological findings were observed in about one third of the patients and pulmonary nodules in about 10% which is similar to data from the literature [25 26]. These findings may represent an opportunity to diagnose and treat unexpected diseases but may also lead to further investigations, increasing costs and potential risks in elderly patients [27]. As it is possible that CXR findings may be delayed relative to symptoms and disease onset, we performed a subgroup analysis to determine if LDCT had a diagnostic advantage in the "short duration of symptoms group" and compared patients presenting within 24h of symptoms onset with patients presenting later. There was no significant diagnostic advantage of LDCT over CXR in the "short duration of symptoms group".

The strengths of our study include the prospective inclusion of 200 consecutive elderly patients with pneumonia in a large teaching hospital. By evaluating their pre- and post-LDCT scan probability of having the disease according to the clinician, we could assess the contribution of LDCT in the diagnosis of pneumonia. A rigorous reference diagnosis was obtained according to international guidelines and the adjudication committee was blinded to LDCT results in order to avoid incorporation bias. Conversely, there are some limitations to this work. First our study was performed in a single center limiting the generalisability of our results. Second, our inclusion criteria did not allow an accurate estimate of under-diagnosis of pneumonia, as only patients with a pneumonia probability warranting an AT were included.

Third, a health economic assessment of the diagnostic imaging tests would have been interesting. The cost of tests is an important aspect and it should be balanced with the consequences of a better classification/diagnosis of patients (not in terms of only clinical outcomes, but also of economic burden). However, our study was not designed for this

purpose, the patients were not randomized and therapeutic decisions were taken by the clinicians with knowledge of the results of both diagnostic tests.

Finally, our choice of a consensus reference diagnosis could be criticised because of its low concordance. However, we used widely accepted definitions of pneumonia and used a systematic approach including independent experts in respiratory medicine, infectious diseases and internal medicine to obtain a consensual reference diagnosis for each case.

Significance of the study and implications for clinicians

The diagnosis of pneumonia is difficult, even more so in elderly patients because of atypical symptoms, alternative diagnoses, and because the reference diagnosis according to international recommendations is debatable and poorly reproducible. The use of LDCT scanning modifies the diagnosis in patients hospitalised for pneumonia even if its availability and cost are limitations, and despite the fact that it is almost impossible to determine if the changes in diagnosis are appropriate in the absence of gold standard. The present results should encourage clinicians to consider performing LDCT in pneumonia diagnostic recommendations in elderly patients, especially in patients with intermediate probability. It can help to exclude a diagnosis of pneumonia, encourage the search for an alternate diagnosis and reduce unnecessary AT. These results should be confirmed in a randomised clinical trial including the discontinuation of antimicrobials in patients with negative LDCT scans.

Acknowledgements

We would like to thank our funders, the patients and their families who volunteered to participate in this study, the clinicians, our research nurses, Ms Marie-Pierre Meynet and Ms Véronique Lachat, the case managers who helped us enrol our participants and our translator, Mr Darren Hart. The study was supported by grants from the Geneva University Hospitals (HUG) (Research & Development Grant, Medical Directorate, HUG) and the Ligue Pulmonaire Genevoise, a non-profit association involved in the home care of patients with respiratory diseases. The contribution of the ESCMID Study Group Elderly Infections (ESGIE, www.escmid.org/esgie) to this study is acknowledged. V Prendki and J Stirnemann conceived the study, wrote the grant to obtain the funding, obtained ethical approval, participated in recruitment, followed the subjects, analysed the results and wrote the manuscript. M Scheffler, X Montet, B Huttner, N Garin, JP Janssens, C Marti, S Carballo, X Roux, C Serratrice, J Serratrice were among the adjudication committee and contributed to the manuscript. F Herrmann and T Agoritsas helped for the statistical plan and the analyses. JL Reny, A Perrier, C Becker, L Kaiser helped design the study and contributed to the manuscript. S Rosset-Zufferey and V Soulier helped recruit the patients, collect data and assisted with patient follow-up. J Stirnemann did the statistical plan and the analyses.

References

1. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 2012;**67**(1):71-79 doi: 10.1136/thx.2009.129502[published Online First: Epub Date]|.
2. Millett ER, Quint JK, Smeeth L, et al. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PloS one 2013;**8**(9):e75131 doi: 10.1371/journal.pone.0075131[published Online First: Epub Date]|.
3. Luna CM, Palma I, Niederman MS, et al. The Impact of Age and Comorbidities on the Mortality of Patients of Different Age Groups Admitted with Community-acquired Pneumonia. Annals of the American Thoracic Society 2016;**13**(9):1519-26 doi: 10.1513/AnnalsATS.201512-848OC[published Online First: Epub Date]|.
4. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2007;**44 Suppl 2**:S27-72 doi: 10.1086/511159[published Online First: Epub Date]|.
5. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;**64**(Suppl 3):iii1-iii55 doi: 10.1136/thx.2009.121434[published Online First: Epub Date]|.
6. Janssens J-P, Krause K-H. Pneumonia in the very old. The Lancet Infectious Diseases 2004;**4**(2):112-24 doi: http://dx.doi.org/10.1016/S1473-3099(04)00931-4[published Online First: Epub Date]|.
7. Faverio P, Aliberti S, Bellelli G, et al. The management of community-acquired pneumonia in the elderly. Eur J Intern Med 2014;**25**(4):312-9 doi: 10.1016/j.ejim.2013.12.001[published Online First: Epub Date]|.
8. Marrie TJ, File TM, Jr. Bacterial Pneumonia in Older Adults. Clinics in geriatric medicine 2016;**32**(3):459-77 doi: 10.1016/j.cger.2016.02.012[published Online First: Epub Date]|.
9. Basi SK, Marrie TJ, Huang JQ, et al. Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcomes. Am J Med 2004;**117**(5):305-11 doi: 10.1016/j.amjmed.2004.03.029[published Online First: Epub Date]|.
10. Hagaman JT, Rouan GW, Shipley RT, et al. Admission chest radiograph lacks sensitivity in the diagnosis of community-acquired pneumonia. The American journal of the medical sciences 2009;**337**(4):236-40 doi: 10.1097/MAJ.0b013e31818ad805[published Online First: Epub Date]|.
11. Esayag Y, Nikitin I, Bar-Ziv J, et al. Diagnostic Value of Chest Radiographs in Bedridden Patients Suspected of Having Pneumonia. The American Journal of Medicine 2010;**123**(1):88.e1-88.e5 doi: http://dx.doi.org/10.1016/j.amjmed.2009.09.012[published Online First: Epub Date]|.
12. Albaum MN, Hill LC, Murphy M, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. Chest 1996;**110**(2):343-50
13. Loeb MB, Carusone SB, Marrie TJ, et al. Interobserver reliability of radiologists' interpretations of mobile chest radiographs for nursing home-acquired pneumonia. Journal of the American Medical Directors Association 2006;**7**(7):416-9 doi: 10.1016/j.jamda.2006.02.004[published Online First: Epub Date]|.
14. Hopstaken RM, Witbraad T, van Engelshoven JM, et al. Inter-observer variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. Clinical radiology 2004;**59**(8):743-52 doi: 10.1016/j.crad.2004.01.011[published Online First: Epub Date]|.
15. Kanwar M, Brar N, Khatib R, et al. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration

rule. Chest 2007;**131**(6):1865-9 doi: 10.1378/chest.07-0164[published Online First: Epub Date]|.
16. Syrjala H, Broas M, Suramo I, et al. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1998;**27**(2):358-63
17. Self WH, Courtney DM, McNaughton CD, et al. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. Am J Emerg Med 2013;**31**(2):401-5 doi: 10.1016/j.ajem.2012.08.041[published Online First: Epub Date]|.
18. Haga T, Fukuoka M, Morita M, et al. Computed Tomography for the Diagnosis and Evaluation of the Severity of Community-acquired Pneumonia in the Elderly. Internal medicine (Tokyo, Japan) 2016;**55**(5):437-41 doi: 10.2169/internalmedicine.55.5556[published Online First: Epub Date]|.
19. Pencina KM, Pencina MJ, D'Agostino RB, Sr. What to expect from net reclassification improvement with three categories. Statistics in medicine 2014;**33**(28):4975-87 doi: 10.1002/sim.6286[published Online First: Epub Date]|.
20. Alba A, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models: Users' guides to the medical literature. JAMA 2017;**318**(14):1377-84 doi: 10.1001/jama.2017.12126[published Online First: Epub Date]|.
21. Claessens YE, Debray MP, Tubach F, et al. Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine 2015;**192**(8):974-82 doi: 10.1164/rccm.201501-0017OC[published Online First: Epub Date]|.
22. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Archives of internal medicine 1997;**157**(13):1453-9
23. Scholze K, Wenke M, Schierholz R, et al. The Reduction in Antibiotic Use in Hospitals. Deutsches Arzteblatt international 2015;**112**(42):714-21 doi: 10.3238/arztebl.2015.0714[published Online First: Epub Date]|.
24. Larke FJ, Kruger RL, Cagnon CH, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. AJR American journal of roentgenology 2011;**197**(5):1165-9 doi: 10.2214/ajr.11.6533[published Online First: Epub Date]|.
25. Jacobs PC, Mali WP, Grobbee DE, et al. Prevalence of incidental findings in computed tomographic screening of the chest: a systematic review. Journal of computer assisted tomography 2008;**32**(2):214-21 doi: 10.1097/RCT.0b013e3181585ff2[published Online First: Epub Date]|.
26. Hall WB, Truitt SG, Scheunemann LP, et al. The prevalence of clinically relevant incidental findings on chest computed tomographic angiograms ordered to diagnose pulmonary embolism. Archives of internal medicine 2009;**169**(21):1961-5 doi: 10.1001/archinternmed.2009.360[published Online First: Epub Date]|.
27. Frank L, Quint LE. Chest CT incidentalomas: thyroid lesions, enlarged mediastinal lymph nodes, and lung nodules. Cancer imaging : the official publication of the International Cancer Imaging Society 2012;**12**:41-8 doi: 10.1102/1470-7330.2012.0006[published Online First: Epub Date]|.

Appendix

Clinicians

In Switzerland physicians can start to work as “assistant” physicians after having obtained their final diploma. Usually, no formal difference is made in the degree of autonomy in decision-making by year of training for “assistant” physicians (usually until a specialty title is obtained). “Assistant” physicians are supervised by a senior physician. In this study, we asked “assistant” physicians to assess the probability of pneumonia before and after LDCT. They were, however, allowed to discuss the probability with the help of their supervising senior physician.

Adjudication committee

After completion of the study, an adjudication committee, blinded to the results of the LDCT scan, retrospectively rated the probability of pneumonia based on all the other available patient records: CXRs, biological and microbiological results, and hospital notes, including the final medical report, but with all references to the LDCT results removed. The committee was composed of eleven board-certified specialists in infectious diseases, respiratory diseases, internal medicine and radiology. All were senior attending physicians with expertise in caring for patients with pneumonia. Each patient’s diagnosis of pneumonia was analysed by the adjudication committee as follows: first, each expert gave an individual opinion of the probability of the patient having pneumonia on a five-point Likert scale (excluded, low, intermediate, high, certain); second, each expert re-examined the cases where the committee had been in disagreement, in full knowledge of the other experts’ first decisions; finally, in plenary session and in the presence of a radiologist, the adjudication committee made consensus decisions on cases that remained unresolved after the first two phases. The adjudication committee’s final decision was considered as the reference diagnosis. The rate of agreement between the adjudication committee’s experts was assessed. Their probabilities of a diagnosis of pneumonia were compared with the pre-LDCT probability.

Tables and figures

Characteristics at baseline	n = 200 *unless stated*	No. (%) or Median (IQR)
Age, years (median, IQR)		84.0 (78.6–90.2)
≥85 years old		93 (46.5%)
Female		100 (50.0%)
Nursing home residents		28 (14.0%)
Body Mass Index in kg/m^2		24.5 (21.5–28.6)
Mini Mental State Examination score	n=162	24 (19–27)
Mini Nutritional Assessment	n=178	8 (6–11)
Functional Independence Measure score	n=171	69 (50–97)
Influenza vaccination within past year	n=182	103 (56.6%)
Pneumococcal vaccination within past 5 years	n=177	7 (4.0%)
Comorbidities		
Hospitalisation during the past 6 months	n=199	70 (35%)
Chronic cardiac disease		103 (51.5%)
Chronic Obstructive Pulmonary Disease		35 (17.5%)
Kidney disease	n=199	60 (30.2%)
Liver disease		11 (5.5%)
Neoplasia		17 (8.5%)
Smoking (past and present)		100 (50.0%)
History of stroke		33 (16.5%)
Cognitive disorders		66 (33.0%)
Swallowing disorders		28 (14.0%)
Poor oral hygiene		38 (19.0%)
Immunosuppressive treatment	n=199	15 (7.5%)
Clinical characteristics of pneumonia		
Type of pneumonia		
Community-Acquired Pneumonia		*162 (81.0%)*
Nursing Home-Acquired Pneumonia		*22 (11.0%)*
Hospital-Acquired Pneumonia (>72 h after hospitalisation)		*16 (8.0%)*
Bronchoaspiration	n=161	12 (7.5%)
Temperature ≥38.0°C		116 (58.0%)
Cough		170 (85.0%)
Dyspnoea		145 (72.5%)
Sputum production		74 (37.0%)
Chest pain		35 (17.5%)
Crackles		171 (85.5%)
Decrease in respiratory sounds		51 (25.5%)
Peripheral Oxygen Saturation, SpO2 <90% on admission		102 (51.0%)
Respiratory rate >20/min on admission		143 (71.5%)
Delirium		92 (46.0%)
Fall		71 (35.5%)
CURB65 score		
1		*36 (18.0%)*
2		*75 (37.5%)*
3		*68 (34.0%)*
4		*21 (10.5%)*
Fine score		102 (89–123)

Table 1. Demographic and clinical characteristics of the 200 patients included in the PneumOLD-CT study at baseline

Laboratory values and vital signs were obtained at hospital admission.

Definitions: immunosuppressive treatment means that patient is under prednisone during more than 15 days or other immunosuppressive drugs. Cognitive disorders were diagnosed after a cognitive consultation (at least CDR 1 dementia) and swallowing disorders were observed during the hospitalization, oral hygiene was defined as good, medium or poor, bronchoaspiration was defined by the clinician according to usual definition.

Abbreviations:

CURB65 is a pneumonia severity score taking into account confusion, respiratory rate, blood pressure, and age 65 or older.

Table 2. Biological, microbiological, radiological characteristics at baseline, and treatment and outcome of the 200 patients included in the PneumOLD-CT study

Characteristics	n = 200 *unless stated*	No. (%) or Median (IQR)
Biological characteristics at baseline		
White blood cell count, $10^3/mm^3$ on admission		11.0 (8.2–14.0)
proBNP, ng/L (range <300 ng/L)	n=170	1836 (667–3801)
C-Reactive Protein, mg/L (range 0–10 mg/L)		84.0 (45.8–159.6)
Procalcitonin, µg/L (range <0.25 ug/L)	n=185	0.33 (0.13–1.30)
Urea, mmol/L		7.9 (6.0–11.9)
Creatinine, µmol/L		97.0 (77.0–133.0)
Albumin, g/L	n=193	35.0 (32.0–38.0)
Prealbumin, mg/L	n=193	122.0 (95.0–162.0)
Microbiological characteristics at baseline		
Positive blood culture	n=192	11 (5.7%)
Positive urinary culture	n=177	82 (46.3%)
Positive sputum culture	n=81	36 (44.4%)
Positive pleural effusion culture	n=6	0
Positive Legionella urinary antigen	n=183	0
Positive pneumococcal urinary antigen	n=178	8 (4.5%)
Positive Legionella pneumophila serology (IgM)		2 (1%)
Positive Chlamydophila pneumoniae serology (IgM)		4 (2%)
Positive Mycoplasma pneumoniae serology (IgM)		3 (1.5%)
Radiological characteristics		
Standing CXR		66 (33%)
Two incidences CXR		63 (31.5%)
Median delay of LDCT		2.2 hours (0.9–15.4)
Good/satisfactory quality according to the radiologist		127 (63.5%)
Radiologist's estimates of the probability of pneumonia		
High		*103 (51.5%)*
Intermediate		*23 (11.5%)*
Low		*74 (37.0%)*
Treatment		
Median duration of antimicrobial therapy		7 days (6–9)
Outcome		
Transfer to intermediate care unit or ICU		13 (7.0%)
30-day mortality		11 (5.4%)
90-day mortality		30 (15.0%)

Abbreviations: CXR for chest x-ray, LDCT for low-dose computed tomography chest scan, ICU for intensive care unit

Table 3. Clinician's estimates of the probability of pneumonia in 200 patients, before and after LDCT chest scans (downgraded probability in green, upgraded probability in red)

		Clinician's estimates of the probability of pneumonia after LDCT					
		Low	Intermediate	High	TOTAL	Change of probability n	Change of probability % [95% CI]
Clinician's estimates of probability of pneumonia before LDCT	Low	10	3	4	**17**	7	41 [18 - 24]
	Intermediate	34	13	23	**70**	57	81 [72 - 90]
	High	13	13	87	**113**	26	23 [15 - 31]
	TOTAL	**57**	**29**	**114**	**200**	**90**	**45 [38 - 52]**

Table 4. Net Reclassification Improvement (NRI) among 200 patients

Clinician's estimates of probability of pneumonia before LDCT	*Clinician's estimates of the probability of pneumonia after LDCT*			**Net reclassification**
	Patients WITH Pneumonia (n=143) according to the adjudication committee			
	Excluded/Low	**Intermediate/High/Certain**		Net reclassification = 6 – 18 = **–12 patients** (–8.4% of the 143 patient with pneumonia)
Excluded/Low	2	6		
Intermediate/High/Certain	18	117		
			143	
	Patients WITHOUT Pneumonia (n=57) according to the adjudication committee			
	Excluded/Low	**Intermediate/High/Certain**		Net reclassification = 29 – 1 = + **28 patients** (+49.1% of the 57 patients without pneumonia)
Excluded/Low	8	1		
Intermediate/High/Certain	29	19		
			57	
	TOTAL patients (n=200)			**Absolute NRI = 28 – 12 = + 16 patients = 8.0% of all 200 patients**

The back cells show patients correctly reclassified by the new model, while the dark grey cells shows patient incorrectly reclassified by the new model. The absolute number of patients correctly reclassified is –12 patients among those with pneumonia, and +28 among those without pneumonia. Overall, the absolute number of patients correctly reclassified is thus +16 patients, corresponding to 8.0% of all patients in our sample.

Table 5. Additional findings following analysis of LDCT chest scan

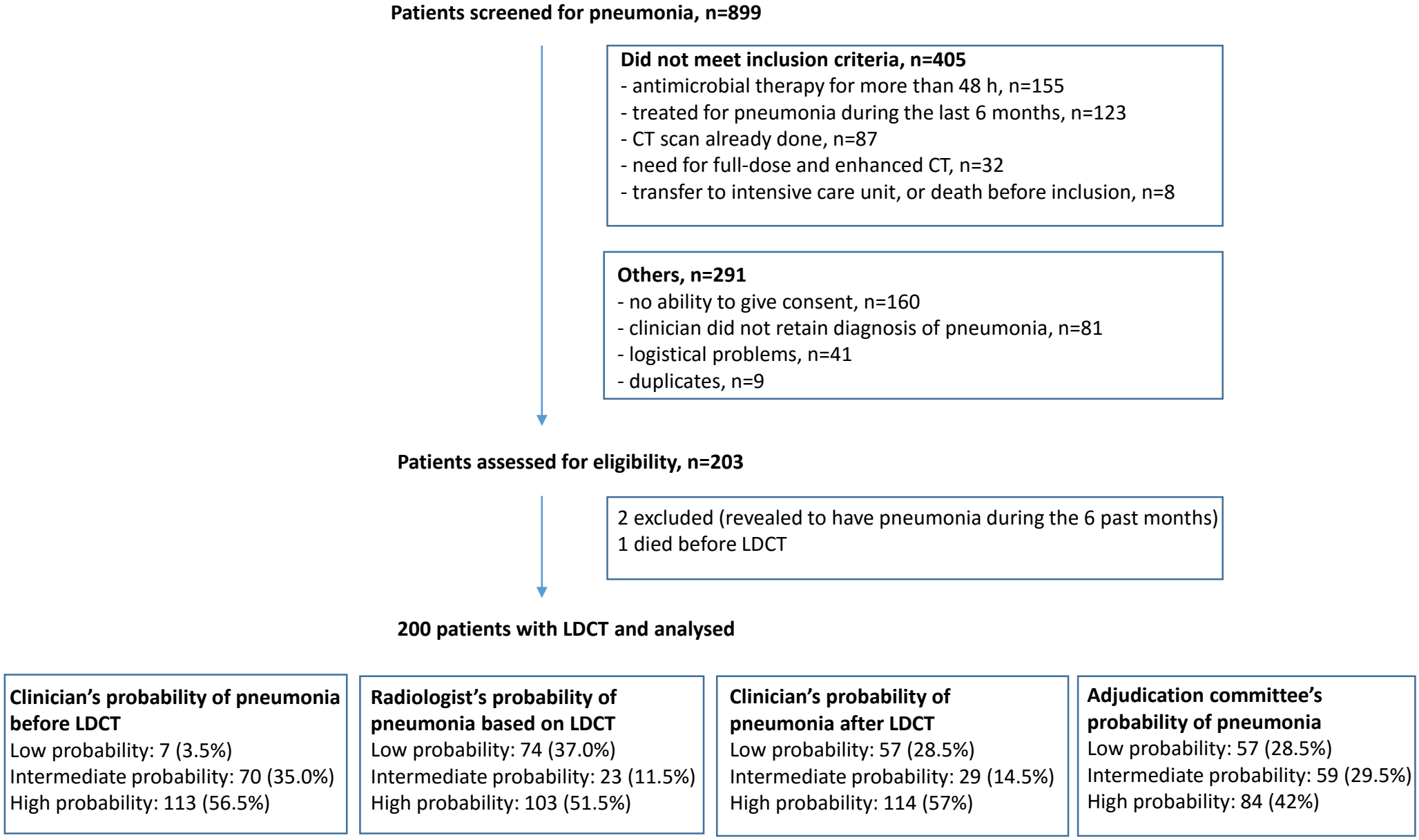
Additional findings	76
Pulmonary findings	51
Pleural effusion	22
Pulmonary nodules	19
Lung mass	1
Lung metastases	1
Emphysema	5
Lung fibrosis	1
Asbestosis	1
Tuberculosis sequelae	1
Other findings	28
Adenomegalies	7
Hepatic lesions	5*
Adrenal nodules	4
Pericardial effusion	3
Abdominal aortic aneurysm	3
Renal cysts	2
Thyroid nodules	1
Fractures	3

*including one hepatic abscess

The same patient could have more than one finding

Table 6. Management of antibiotic in patients with a low post-LDCT probability of pneumonia

Patients with a low probability of pneumonia after LDCT	**57**	
Appropriate management of antibiotics	46	
-discontinuation	*17*	
-continuation because of a differential diagnosis	*29*	*14 patients with BPCO, 12 with urinary infection, 2 with digestive sepsis, 1 with febrile neutropenia*
Inappropriate continuation of antibiotics	11	


Patients screened for pneumonia, n=899
Did not meet inclusion criteria, n=405
- antimicrobial therapy for more than 48 h, n=155
- treated for pneumonia during the last 6 months, n=123
- CT scan already done, n=87
- need for full-dose and enhanced CT, n=32
- transfer to intensive care unit, or death before inclusion, n=8
Others, n=291
- no ability to give consent, n=160
- clinician did not retain diagnosis of pneumonia, n=81
- logistical problems, n=41
- duplicates, n=9
Patients assessed for eligibility, n=203
2 excluded (revealed to have pneumonia during the 6 past months)
1 died before LDCT
200 patients with LDCT and analysed
Clinician's probability of pneumonia before LDCT
Low probability: 7 (3.5%)
Intermediate probability: 70 (35.0%)
High probability: 113 (56.5%)
Radiologist's probability of pneumonia based on LDCT
Low probability: 74 (37.0%)
Intermediate probability: 23 (11.5%)
High probability: 103 (51.5%)
Clinician's probability of pneumonia after LDCT
Low probability: 57 (28.5%)
Intermediate probability: 29 (14.5%)
High probability: 114 (57%)
Adjudication committee's probability of pneumonia
Low probability: 57 (28.5%)
Intermediate probability: 59 (29.5%)
High probability: 84 (42%)

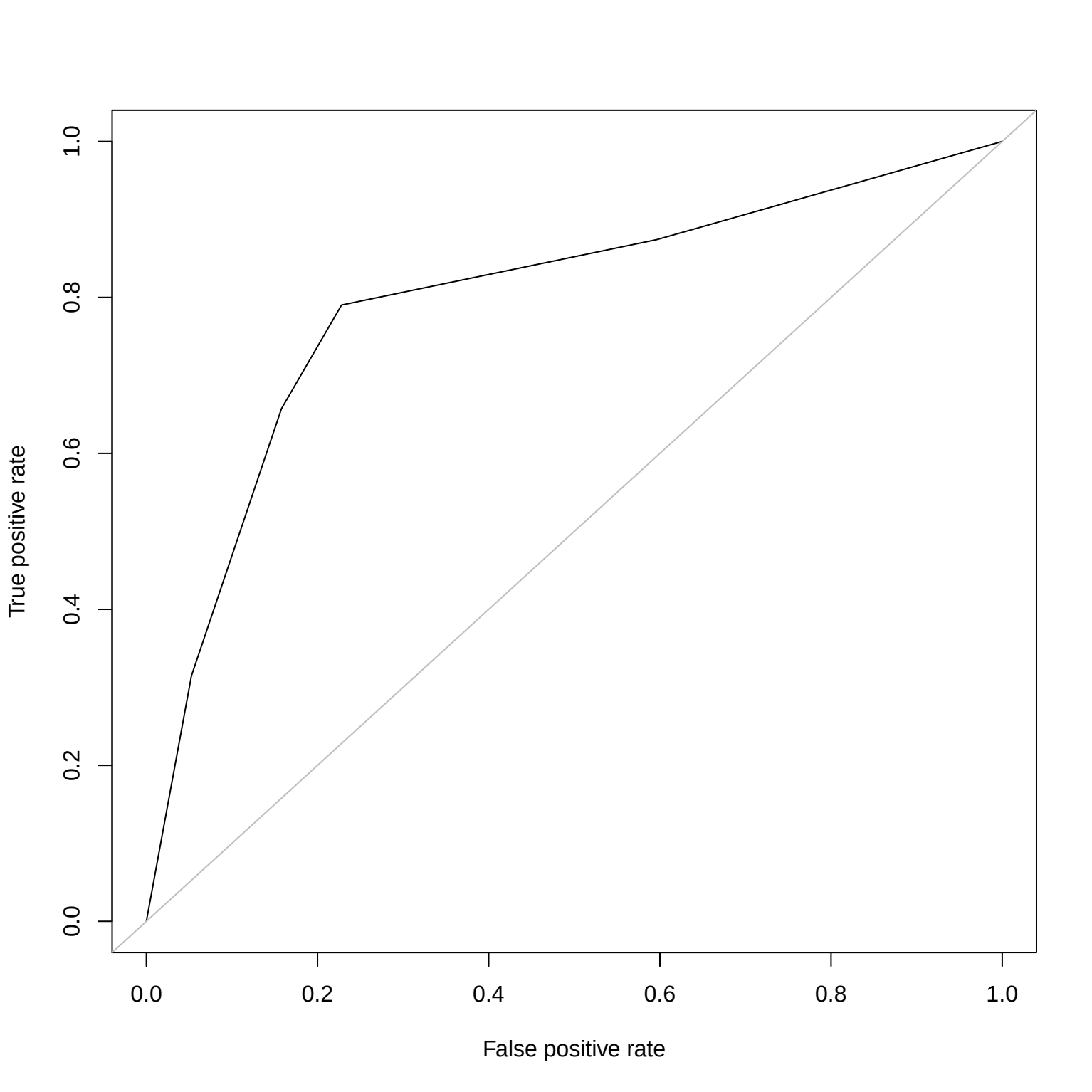

True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0

Figure 3. ROC curve of the post-LDCT probability of a diagnosis of pneumonia compared with the reference diagnosis