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# Ultra-low-dose CT versus chest X-ray for patients suspected of pulmonary disease at the emergency department: a multicentre randomised clinical trial

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## ABSTRACT

**Background** Chest CT displays chest pathology better than chest X-ray (CXR). We evaluated the effects on health outcomes of replacing CXR by ultra-low-dose chest-CT (ULDCT) in the diagnostic work-up of patients suspected of non-traumatic pulmonary disease at the emergency department.

**Methods** Pragmatic, multicentre, non-inferiority randomised clinical trial in patients suspected of non-traumatic pulmonary disease at the emergency department. Between 31 January 2017 and 31 May 2018, every month, participating centres were randomly allocated to using ULDCT or CXR. Primary outcome was functional health at 28 days, measured by the Short Form (SF)-12 physical component summary scale score (PCS score), non-inferiority margin was set at 1 point. Secondary outcomes included hospital admission, hospital length of stay (LOS) and patients in follow-up because of incidental findings.

**Results** 2418 consecutive patients (ULDCT: 1208 and CXR: 1210) were included. Mean SF-12 PCS score at 28 days was 37.0 for ULDCT and 35.9 for CXR (difference 1.1; 95% lower CI: 0.003). After ULDCT, 638/1208 (52.7%) patients were admitted (median LOS of 4.8 days; IQR 2.1–8.8) compared with 659/1210 (54.5%) patients after CXR (median LOS 4.6 days; IQR 2.1–8.8). More ULDCT patients were in follow-up because of incidental findings: 26 (2.2%) versus 4 (0.3%).

**Conclusions** Short-term functional health was comparable between ULDCT and CXR, as were hospital admissions and LOS, but more incidental findings were found in the ULDCT group. Our trial does not support routine use of ULDCT in the work-up of patients suspected of non-traumatic pulmonary disease at the emergency department.

**Trial registration number** NTR6163.

## INTRODUCTION

While chest X-ray (CXR) is a standard diagnostic procedure in patients suspected of non-traumatic

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies underscore the higher diagnostic accuracy of chest CT as compared with chest X-ray (CXR), but since no patient outcome measures were collected, the effectiveness of both strategies cannot be compared.

## WHAT THIS STUDY ADDS

⇒ Our randomised trial is unique in its aim to assess the yield of replacing CXR by ultra-low-dose chest-CT (ULDCT) in the diagnostic work-up of emergency department patients suspected of non-traumatic pulmonary disease in terms of patient outcomes and healthcare efficiency. We showed that ULDCT leads to functional health outcomes at 28 days that are at least similar to those obtained if management is guided by CXR, while resulting in minimal differences in hospital admission rates, length of stay and mortality rates.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The results of our study enforces the current guidelines that adhere to CXR as first-line imaging technique. Future research should focus on subgroups of patients that might benefit of ULDCT.

pulmonary disease at the emergency department (ED), chest CT highlights chest pathology better than CXR.<sup>1 2</sup> Studies in patients with possible community-acquired pneumonia (CAP) and other non-traumatic pulmonary diseases have demonstrated that the diagnostic accuracy of CXR is limited.<sup>3–6</sup> Three studies showed CT markedly

improved diagnostic accuracy, and subsequently changed diagnoses and clinical management.<sup>4 5 7</sup> CT also requires more radiation and increases the risk of radiation-induced cancer.<sup>8 9</sup> Ultra-low-dose chest-CT (ULDCT; dose <1 mSv) has overcome this disadvantage, while preserving diagnostic accuracy for many acute pulmonary diseases that present at the ED, like pneumonia and congestive heart failure.<sup>10 11</sup>

The use of ULDCT reduced false-positive and false-negative CXR findings with consequences for clinical management by 20% in a prospective study in an outpatient setting.<sup>7</sup> Yet ULDCT is still more expensive and less accessible than CXR, and incidental findings are more prevalent.<sup>12 13</sup> While the superior diagnostic accuracy could lead to faster detection of underlying conditions and timely initiation of effective treatment, incidental findings detected on ULDCT could also complicate healthcare processes, potentially prolonging hospital stay.<sup>5</sup>

The value of a diagnostic test is not expressed by its accuracy but depends on how it affects patients health.<sup>14</sup> New tests should only be introduced into clinical practice when they have demonstrated to impact clinical decision-making, resulting in better patient health outcomes or a simplification of the healthcare process.<sup>15</sup> Diagnostic imaging technologies that affect large numbers of patients and hold the potential to substantially increase healthcare costs require more extensive and more robust data on outcomes than those without these attributes.<sup>16</sup>

At present, there is no direct evidence that patient management in the ED guided by chest-(ULD)CT rather than CXR results in better patient outcomes or a more efficient process of care; for example, with fewer or shorter hospital admissions. We designed a multicentre non-inferiority randomised clinical trial in which we randomly allocated consenting ED patients suspected of non-traumatic pulmonary disease to either ULDCT or CXR.

The link between imaging and health outcomes is an indirect one, and superior accuracy is not guaranteed to lead to improved health outcomes.<sup>16</sup> We did not expect ULDCT to lead to better patient outcomes but anticipated that it would result in functional health after 28 days at least as good as obtained with CXR, hence the non-inferiority design. In addition, we hypothesised that improved detection of underlying conditions with ULDCT would lead to a more efficient healthcare process, reflected in fewer hospital admissions and a shorter hospital length of stay, compared with CXR.

## METHODS

### Study design

In this pragmatic, multicentre, non-inferiority randomised clinical trial we compared patient outcomes and short-term health process parameters after ULDCT to those after CXR in ED patients suspected of non-traumatic pulmonary disease. The protocol and statistical analysis plan for this trial on the OPTimal IMAGING strategy in patients suspected of non-traumatic pulmonary disease at the ED: chest X-ray or CT (OPTIMACT) have been published earlier.<sup>17 18</sup> In short, during randomly assigned periods of one calendar month between 31 January 2017 and 31 May 2018, either ULDCT or conventional CXR was used in two participating Dutch hospitals: one university hospital (Amsterdam UMC) and one large teaching hospital (Spaarne Gasthuis).

The trial was performed according to General Data Protection Regulation and Good Clinical Practice standards. Written informed consent was provided by all study participants. This study report was prepared following the CONSolidated Standards Of Reporting Trials (CONSORT) reporting guidelines, using the extension for non-inferiority and equivalence randomised trials.<sup>19</sup>

### Setting and participants

Eligible for inclusion were ED patients aged 18 years and older, suspected of non-traumatic pulmonary disease and requiring CXR according to the attending physician. Patients could be either self-referred or referred by a general practitioner or their treating physician at the hospital. Excluded were patients unable to undergo ULDCT or CXR, incapacitated patients, pregnant women and patients with a life expectancy less than 1 month or with other anticipated barriers to 28-days follow-up data collection; subjects could only participate once.

### Study procedures

History taking, physical examination and laboratory tests were initiated by the attending physician. After setting the indication for chest imaging and acquiring informed consent, the attending physician provided a working diagnosis on the structured and standardised radiology request form. This was followed by either ULDCT or CXR, according to the imaging method allocated to the month of presentation. If the clinical question was not adequately answered after obtaining the CXR or ULDCT, standard additional imaging (eg, chest CT with intravenous contrast medium, CT pulmonary angiography) was performed. If there was a high suspicion of pulmonary emboli at ED admission, patients directly underwent a CT pulmonary angiography, in accordance with regular clinical practice. The technical aspects of the imaging methods can be found in the study protocol paper and online supplemental text S1.<sup>17</sup>

Radiologists used a structured standardised report to optimise and standardise reading. Reading and reporting was performed or supervised by the radiologist on call at the time of clinical management, also outside office hours. The ULDCT and CXR were read with prior imaging if available. To increase inter-reader consistency, the residents and radiologist less experienced in the field of chest imaging were supervised by a group of seven radiologists with a subspecialty in chest imaging. The attending physician subsequently formulated an ED discharge diagnosis. Decisions on additional imaging, treatment, hospital admission and discharge were at the discretion of the attending physician, according to national guidelines, if applicable.

### Data collection

Baseline ED data included medical history and physical examination, laboratory, microbiological and radiological test results, diagnosis at ED discharge, prescription of antibiotics or diuretics and hospital admission. Follow-up data after ED discharge included disease course, treatment outcome, additional imaging, hospital length of stay, mortality up to day 28 and patients in follow-up after day 28 because of incidental findings. All data were obtained from electronic patient records.

Whenever necessary, additional information was obtained from general practitioners, nursing wards, outpatient clinics or hospitals where patients had been transferred or referred to. Twenty-eight days after ED presentation study participants received the Short Form (SF)-12 questionnaire; the questionnaires were available in Dutch and English and in electronic and paper form. We prompted with frequent reminders to ensure maximum response.

We assigned one or more final diagnoses after 28 days of follow-up, based on a review of all clinical, radiological and microbiological data available. For this purpose, a diagnostic handbook was developed enabling standardised and reproducible categorisation for 32 diagnoses. More details on the methodology of the handbook, its evaluation and validation are

available elsewhere.<sup>20</sup> Patients in whom the day 28 diagnosis could be assigned were also assigned an ED discharge diagnosis.

All baseline and follow-up data and questionnaires responses were coded and saved in electronic Case Report Forms (Castor EDC, Amsterdam, The Netherlands).

## Outcomes

Considering the wide range of conditions and underlying diagnoses, we selected a generic health-related outcome measure with minimal burden for study participants. The primary outcome was functional health at day 28 after ED presentation, as measured by the physical component summary scale (PCS) score of the SF-12 questionnaire V.1 (scale 0–100, higher score corresponds to better functional health).<sup>21</sup> Secondary outcomes included hospital admission, hospital length of stay, mortality within 28 days, number of patients requiring follow-up because of incidental findings on ULDCT or CXR after 28 days and mental health measured by the mental component summary scale (MCS) score of the SF-12 (scale 0–100).<sup>21</sup> An economic evaluation will be reported elsewhere.

## Statistical analysis

We evaluated all effects in those who underwent the allocated imaging method. We express the effect of imaging as an absolute mean difference in the SF-12 PCS score, with a 95% lower CI. A one-point difference in the mean SF-12 PCS score was defined as the non-inferiority margin.

The primary analyses were done using all available data, with sensitivity analyses using multiple imputation of missing

questionnaire responses (using age and sex as predictors) and to adjust for confounding. Since we anticipated non-response of the SF-12 questionnaires, we analysed differences in baseline characteristics between responders and non-responders.

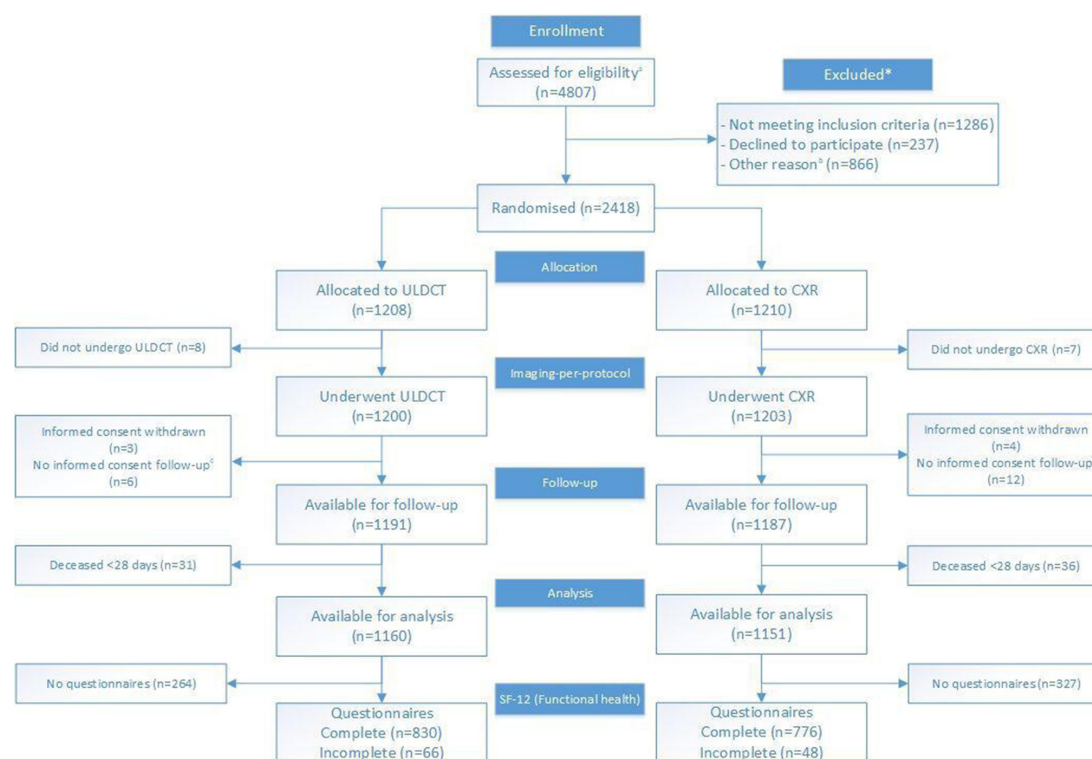
We express all effects on secondary outcomes as differences between groups with two-sided 95% CIs. We hypothesised that replacing CXR by ULDCT would lead to a more efficient healthcare process, reflected in fewer admissions and a shorter hospital length of stay. We calculated the median hospital length of stay and the difference between groups in those admitted using the Hodges-Lehmann estimator. The effect on mortality within 28 days was expressed as an absolute risk difference. The effect on incidental findings is reported as the absolute difference in proportions of patients in follow-up. All analyses were performed in SPSS V.26.

An SD of 10 on the SF-12 was anticipated.<sup>22</sup> A power analysis showed that using a 0.05 significance level, 2400 participants were needed to achieve 80% power in excluding a 1 point lower mean SF-12 PCS score for ULDCT, using the two-sample t-test statistic, assuming no actual difference in the mean scores. This 1-point non-inferiority margin comes down to a 0.1 effect size.

## RESULTS

### Participants

4807 patients presented at the ED with suspected non-traumatic pulmonary disease (figure 1). Of these, 2418 were included: 1208 were allocated to ULDCT and 1210 to CXR (online supplemental table S1 for information on the total eligible group and online supplemental figure S1 for location and month of



**Figure 1** Trial profile. CXR, chest X-ray; SF-12, Short Form 12; ULDCT, ultra-low-dose chest-CT. <sup>a</sup> Due to privacy regulations the total number of patients assessed for eligibility, and the total number of patients excluded for randomisation are incomplete. These numbers are composed of complete data (Amsterdam UMC, location AMC) and data from a random sample of non-included patients (Spaarne Gasthuis). Specified in online supplemental table 1. <sup>b</sup> Specified in online supplemental table 1. <sup>c</sup> Short informed consent form signed at the emergency department as patient was too ill for full consent, giving permission to use imaging information for study purposes. No full informed consent form, giving permission for collection of follow-up information was signed.



**Table 1** Baseline characteristics of study participants\*†

	ULDCT (n=1208)	CXR (n=1210)
Mean age (±SD), years	59.0 (18.1)	59.0 (18.6)
Female sex	613 (50.7)	587 (48.5)
Comorbidity		
Charlson Comorbidity Index (IQR)‡	3.0 (1.0–5.0)	3.0 (1.0–5.0)
Immunocompromised	285 (23.6)	246 (20.3)
Malignancy§	229 (19.0)	222 (18.3)
Diabetes§	230 (19.0)	245 (20.2)
Pulmonary disease		
Chronic obstructive pulmonary disease§	175 (14.5)	179 (14.8)
Asthma	141 (11.7)	109 (9.0)
Interstitial lung disease	29 (2.4)	28 (2.3)
Cystic fibrosis	14 (1.2)	14 (1.2)
Cardiac disease		
Myocardial infarction§	159 (13.2)	169 (14.0)
Chronic cardiac failure§	98 (8.1)	98 (8.1)
Neurological disease§	140 (11.6)	149 (12.3)
Kidney disease§	104 (8.6)	119 (9.8)
Thromboembolic disease	92 (7.6)	107 (8.8)
Presenting symptoms		
Dyspnoea	663 (54.9)	695 (57.4)
Cough	679 (56.2)	631 (52.1)
Fever	514 (42.5)	468 (38.7)
Thoracic pain	442 (36.6)	460 (38.0)
Sputum production	378 (31.3)	354 (29.3)
Haemoptysis	54 (4.5)	41 (3.4)
Confusion	50 (4.1)	41 (3.4)
Clinical question on radiology request form		
Pneumonia	837 (69.3)	822 (67.9)
Pulmonary congestion	76 (6.3)	114 (9.4)
Bronchitis	108 (8.9)	57 (4.7)
Pneumothorax	36 (3.0)	69 (5.7)
Pleural effusion	35 (2.9)	46 (3.8)
Pulmonary tumour	10 (0.8)	10 (0.8)
Atelectasis	4 (0.3)	3 (0.3)
Pulmonary metastases	4 (0.3)	3 (0.2)
Other	90 (7.5)	(6.5)

\*See online supplemental table S5 for a detailed composition of this table including specification of variables.

†Values are numbers (percentages) unless otherwise specified.

‡Charlson Comorbidity Index, excluding AIDS. Predicts 10-year survival in patients with multiple comorbidities.<sup>32</sup>

§Variables included in the Charlson Comorbidity Index.<sup>32</sup>

CXR, chest X-ray; ULDCT, ultra-low-dose chest CT.

inclusion). Baseline characteristics of included patients were comparable between groups (table 1). Presenting symptoms and clinical indication on the radiology request form were largely similar, although slightly more ULDCT patients presented with cough and fever and had bronchitis as possible diagnosis (table 1).

Eight ULDCT and seven CXR patients did not undergo the allocated imaging method. Another 92 patients (40 ULDCT

and 52 CXR) only signed a short informed consent, retracted their informed consent during follow-up or died within 28 days, leaving 1160 ULDCT patients and 1151 CXR patients available for analysis of the primary outcome (figure 1).

The results of ULDCT and CXR were directly communicated to the attending physician by phone. Clinical management was based on the initial report. In only 1.0% of ULDCTs and 0.6% of CXRs the initial report was adjusted by the supervisor, this was directly communicated with the attending physician. Information on the availability of prior imaging can be found in online supplemental text S2.

The median ULDCT radiation dose was 0.2 mSv (IQR 0.2–0.3 mSv). The median CXR dose was for portable anterior posterior (AP) CXR 0.02 mSv (IQR 0.02–0.03 mSv) and bucky CXR posterior anterior (PA) and lateral 0.05 mSv (IQR 0.03–0.07 mSv).

### Management at the emergency department

More patients in the ULDCT group had a clinical diagnosis of CAP at ED discharge: 255/1161 (22.0%) versus 189/1151 (16.4%), a difference of 5.5% (95% CI: 2.3% to 8.8%). In the ULDCT group, more patients had a diagnosis at ED discharge of (possible) influenza A/B (table 2).

The number of clinically relevant incidental findings was 100 (8.3%; 95% CI: 7.0% to 10.0%) in the ULDCT group versus 14 (1.2%; 95% CI: 1.0% to 2.0%) in the CXR group (absolute difference 7.2; 95% CI: 5.5 to 8.9). The most frequently reported incidental findings were pulmonary nodules (ULDCT 54 and CXR 7; online supplemental table S2).

In the ULDCT group 475/1208 patients (39.3%) had one or more additional imaging procedures within 28 days after the initial ULDCT, compared with 652/1210 (53.9%) in the CXR group after the initial CXR, an absolute difference of –14.6% (95% CI: –18.5% to –10.6%).

In the ULDCT group median ED length of stay was 4:47 hours (IQR 3:39–6:21). For CXR median ED length of stay was 4:36 hours (IQR 3:22–6:14). In the ULDCT group 638/1208 (52.7%) patients were admitted to hospital, with a median hospital length of stay of 4.8 days (IQR 2.1–8.8). After CXR 659/1210 (54.5%) patients were admitted to hospital; their median hospital length of stay was 4.6 days (IQR 2.1–8.8). There was a significant difference in the median ED length of stay (0:14 hours, IQR 0:04–0:23) in favour of ULDCT, there was no significant difference in the proportion admitted (1.7%; 95% CI: –0.06 to 0.02) or in the median hospital length of stay between both groups (0.04 days; 95% CI: –0.3 to 0.5). After ULDCT 50/1208 patients (4.1%) were admitted to the intensive care unit versus 44/1210 (3.6%) patients in the CXR group.

### Outcomes

In the ULDCT group 896/1160 (77.2%) of the SF-12 questionnaires were returned (830 complete and 66 incomplete) versus 824/1151 (71.6%) for CXR (776 complete and 48 incomplete). There were only minor differences in baseline characteristics between responders and non-responders (online supplemental tables S3 and S4). Functional health measured by the mean PCS score was 37.0 (SD: 11.1, 95% CI: 36.2 to 37.8) in the ULDCT group compared with 35.9 (SD: 10.6, 95% CI: 35.2 to 36.7) in the CXR group, a difference of 1.1 points (95% lower CI: 0.003) and demonstrating non-inferiority of ULDCT (figure 2, online supplemental figure S2). A sensitivity analysis including 109 imputed PCS scores of partially incomplete questionnaires showed results similar to the primary analysis, with a mean PCS

**Table 2** Diagnoses at ED discharge and at Day 28\*†

Diagnosis	ULDCT (n=1161)		CXR (n=1151)		Difference (95% CI)	
	Diagnosis at ED discharge	Diagnosis at Day 28	Diagnosis at ED discharge	Diagnosis at Day 28	Diagnosis at ED discharge	Diagnosis at Day 28
Community-acquired pneumonia	255 (22.0)	225 (19.4)	189 (16.4)	169 (14.7)	5.5 (2.3 to 8.8)	4.7 (1.6 to 7.8)
Lower respiratory tract infection other than pneumonia	101 (8.7)	121 (10.4)	100 (8.7)	116 (10.1)	0 (−2.3 to 2.3)	0.3 (−2.1 to 2.8)
COPD exacerbation	83 (7.1)	116 (10.0)	72 (6.3)	127 (11.0)	0.8 (−1.1 to 2.9)	−1.0 (−3.5 to 1.5)
(Possible) influenza A/B‡	74 (6.4)	96 (8.3)	37 (3.2)	73 (6.3)	3.2 (1.4 to 4.9)	1.9 (−0.2 to 4.0)
Congestive heart failure	66 (5.7)	66 (5.7)	87 (7.6)	110 (9.6)	−1.9 (−3.9 to 1.5)	−3.9 (−6.0 to −1.7)
Asthma exacerbation	51 (4.4)	75 (6.5)	34 (3.0)	49 (4.3)	1.4 (−0.1 to 3.0)	2.2 (0.4 to 4.0)
Upper respiratory tract infection	49 (4.2)	52 (4.5)	48 (4.2)	64 (5.6)	0 (−1.6 to 1.7)	−1.1 (−2.9 to 0.7)
Healthcare-associated pneumonia	4 (0.3)	50 (4.3)	8 (0.7)	37 (3.2)	−0.4 (−0.9 to 0.2)	1.1 (−0.5 to 2.6)
Extra-thoracic pathology	259 (22.3)	299 (25.8)	246 (21.4)	338 (29.4)	0.9 (−2.4 to 4.3)	−3.6 (−7.3 to 0.03)
Thoracic pain of unknown origin	110 (9.5)	122 (10.5)	112 (9.7)	135 (11.7)	−0.3 (−2.7 to 2.2)	−1.2 (−3.8 to 1.3)
Fever of unknown origin	111 (9.6)	53 (4.6)	85 (7.4)	46 (4.0)	2.2 (−0.1 to 4.4)	0.6 (−1.1 to 2.2)
Other thoracic pathology	57 (4.9)	60 (5.2)	66 (5.7)	63 (5.5)	−0.8 (−2.7 to 1.0)	−0.3 (−2.1 to 1.5)
No definite diagnosis yet	78 (6.7)	–	108 (9.4)	–	−2.7 (−4.9 to 0.5)	–

\*Values are numbers (percentages) unless otherwise noted.

†Only diagnoses that occurred in more than 50 patients either at ED discharge or at Day 28 are reported in this table. See online supplemental table S6 for the results of all 32 diagnostic categories. Patients could have more than one diagnosis.

‡(Possible) influenza A/ B: at ED discharge a diagnosis of possible influenza was assigned if a patient was treated for influenza A/B awaiting the results of the PCR test. At day 28 diagnosis of influenza A/B was assigned to PCR positive patients accordingly.

.COPD, chronic obstructive pulmonary disease; CXR, chest X-ray; ED, emergency department; ULDCT, ultra-low-dose chest-CT.

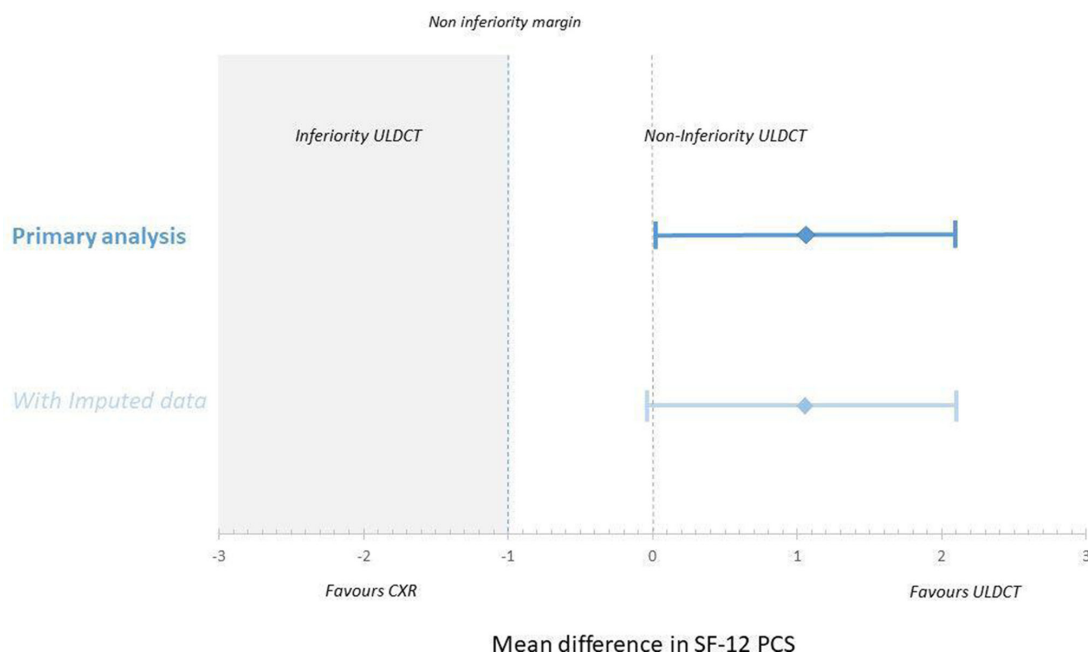
score 36.9 in the ULDCT group (n=892) versus 35.9 in the CXR group (n=823), a difference of 1.0 (one-sided 95% lower CI: −0.06). Additional sensitivity analyses did not produce substantially different findings (online supplemental text S3, figure 2).

In 66/2378 patients who gave permission for follow-up (2.8%; 30 ULDCT and 36 CXR) insufficient follow-up data were available to assign the day 28 diagnosis, leaving 1161 ULDCT and 1151 CXR patients. With ULDCT, more patients had a day 28 diagnosis of CAP and asthma exacerbation, while patients in the

CXR group more often had a day 28 diagnosis of congestive heart failure (table 2).

At day 28, 26 ULDCT patients (2.2%; 95% CI: 1.0% to 3.0%) and four CXR patients (0.3%; 95% CI: 0.0% to 1.0%) were in follow-up because of clinically relevant incidental findings (absolute difference 1.8; 95% CI: 1.0 to 2.7). Of these, three ULDCT patients and two CXR patients were lost to follow-up.

Mental health measured by the mean MCS score for ULDCT was 46.2 (95% CI: 44.5 to 46.0) versus 45.2 (95% CI: 45.5 to



**Figure 2** Equivalence plot of the physical component summary scale (PCS) scores of the Short Form (SF)-12 questionnaires. CI primary analysis: 0.003 to 2.13 (difference is 1.1) and CI imputed data: −0.06 to 2.10 (difference is 1.0). CXR, chest X-ray; ULDCT, ultra-low-dose chest-CT.

46.9) for CXR, a mean difference of 1.0 (95% CI: -0.1 to 2.0). Mortality rates within 28 days were 2.6% for ULDCT and 3.0% for CXR, resulting in an absolute risk difference of 0.4% (95% CI: -0.9% to 1.7%).

## DISCUSSION

In this trial, we showed that using ULDCT in the diagnostic work-up of patients suspected of non-traumatic pulmonary disease at the ED resulted in functional health outcomes at 28 days that are at least similar to those obtained with management guided by CXR, with minimal differences in ED length of stay, hospital admissions, hospital length of stay and mortality rates, less additional imaging but more incidental findings.

CAP was more often diagnosed at ED discharge, with subsequent confirmation of diagnosis at day 28, in the ULDCT group, reflecting the higher accuracy of ULDCT for CAP.<sup>12,5,6</sup> However, this hardly affected clinical management. These results are in line with a previous prospective study comparing clinical management and outcomes in adults hospitalised with CAP who had radiological evidence of pneumonia on chest-CT but not on CXR, as compared with patients with radiological evidence on CXR. The 66/2251 (2.9%) patients with only evidence of pneumonia on chest-CT had management and clinical outcomes comparable to CXR patients.<sup>23</sup>

Similarly, congestive heart failure was more often diagnosed with CXR at day 28. The presumed reason for underdiagnosing congestive heart failure with ULDCT was unfamiliarity of radiologists to detect congestive heart failure on ULDCT in the ED setting.

The similarity in health outcomes with CXR and ULDCT, despite the well-documented lower diagnostic accuracy of CXR,<sup>12,5-7</sup> is likely explained by CXR's ability to detect the most relevant diagnoses in ED patients.<sup>24</sup> In case a presumed clinical diagnosis is not confirmed by CXR, the attending physician may decide to prompt treatment nonetheless, or perform additional imaging. Indeed, in our study CXR patients underwent significantly more additional imaging procedures within 28 days than in ULDCT patients.

As expected, more ULDCT patients had incidental findings and more were in follow-up because of these findings at 28 days, mostly due to pulmonary nodules. The number of clinically relevant incidental pulmonary nodules and patients in follow-up at day 28 is lower than in previous studies. In a retrospective study of 1000 CT pulmonary angiographies ordered at the ED in a group of patients with an age distribution comparable to our ULDCT cohort, 9.9% of the patients with incidental pulmonary nodules required follow-up, compared with 4.1% in our study (online supplemental table S2).<sup>25</sup> This difference is very likely due to differences in comorbidities between both cohorts.

The use of computer-aided diagnosis for lung nodule detection can aid in the detection and follow-up of clinically relevant incidental pulmonary nodules, especially in the hectic work environment of the ED, but the software was not yet available in the radiology departments during our trial. Further studies should evaluate the added value of artificial intelligence in this setting. The impact of incidental findings on long-term functional health could not be assessed in our trial because of the limited follow-up period.

As our study included consecutive ED patients, study limitations are mostly inherent to the demanding workflow at the ED, which sometimes interfered with obtaining informed consent and the logistics to perform ULDCT. Due to the pragmatic nature of this trial, concealment of allocation was not possible. This could

have potentially led to information and selection biases. It may explain the higher number of patients with a clinical suspicion of bronchitis for ULDCT and the higher number of patients with possible pulmonary congestion and pneumothorax for CXR. The higher number of patients with a baseline comorbidity of asthma in the ULDCT group, and the resulting higher number of patients with a day 28 diagnosis of asthma exacerbation in the ULDCT group, are probably due to a seasonal increase of asthma exacerbations in the months February, March and April, when ULDCT was more often the allocated method.<sup>26</sup> However, the similarity in baseline characteristics and presenting symptoms in both study groups indicates that this was unlikely to result in a systematic bias in our study. The SF-12 questionnaire response (ULDCT 77.2% and CXR 71.6%) was, despite many efforts, lower than anticipated but higher than in earlier studies at the ED.<sup>27,28</sup> However, there were only minor differences in baseline characteristics between responders and non-responders (online supplemental tables 2 and 3).

We designed this study as a non-inferiority trial, since we anticipated that the superior accuracy of ULDCT would lead to health outcomes at least as good as after CXR, with a more efficient healthcare process. The point estimate of the mean difference between the two groups shows a 1.1 point difference in mean PCS score in favour of ULDCT. With more returned questionnaires, the precision in this estimate would have been larger and power increased, potentially demonstrating statistically significant superiority of the ULDCT strategy. However, we believe that as difference of 1.1 in mean the PCS-score found is close to the prespecified non-inferiority margin of 1 point and unlikely to be of clinical relevance.

Multiple radiologists with different levels of experience in chest imaging were involved in reading the ULDCT and CXR examinations for this study. This has caused inter-reader variability, although the low proportion of initial reports adjusted by the supervisor (1.0% ULDCTs and 0.6% CXRs) shows that reporting was largely consistent.

This study was performed before the outbreak of the corona virus infectious disease-19 (COVID-19) pandemic. The pandemic changed the incidence, presentation and management of patients suspected of CAP compared with the usual situation, which is not accounted for in our study.<sup>29</sup>

To our knowledge, this large-scale pragmatic randomised trial is unique in its aim to assess the yield of replacing CXR by ULDCT in the diagnostic work-up of ED patients suspected of non-traumatic pulmonary disease, not in terms of diagnostic accuracy, but in terms of short-term patient outcomes and healthcare efficiency. Participants were included in an urban university hospital and a suburban teaching hospital ensuring an unselected, mixed study population, making results widely applicable. The development and use of the diagnostic handbook adds to the consistency of disease classification and can also be considered one of the strengths of our approach.<sup>20</sup>

Improved diagnostic accuracy on itself does not automatically translate to improved patient outcomes, as the impact of imaging depends on the outcome of clinical interventions that follow.<sup>16</sup> It is therefore argued that significant changes in treatment planning and a meaningful change in patient outcome should be documented for new radiological applications to be accepted.<sup>30</sup> Our study showed that ULDCT leads to no marked effect on healthcare efficiency, in terms of number of admissions and hospital length of stay or on short-term health outcomes, in the broad population of ED patients suspected of non-traumatic pulmonary disease. Furthermore, ULDCT has higher immediate imaging costs than CXR while both the examination and reading



require more time, which might be a disadvantage at a busy ED. The findings in this trial enforce the current guidelines which adhere to CXR as first-line imaging technique in ED patients suspected of non-traumatic pulmonary disease.<sup>31</sup>

## CONCLUSION

Considering the availability and costs of ULDCT, the results of our trial do not support the routine use of ULDCT in the work-up of patients presenting with non-traumatic pulmonary disease at the ED.

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**Contributors** JS and JMP were the principal investigators of the trial and contributed equally. JS and JMP were involved in design, planning and execution of the trial, data interpretation and drafting of the manuscript. IAHvdb and MMNPK were involved in design, planning and execution of the trial, data acquisition, data analysis, data verification, data interpretation and drafting of the manuscript. IAHvdb and MMNPK contributed equally. TSrVt was involved in design, planning and execution of the trial, data acquisition, data analysis and data interpretation and revised the manuscript critically. PMB, MGWD and SB were involved in design, planning, data analysis and drafting of the manuscript. JTA, LFMB, MG, SM, ADMVs and MLR were involved in planning of the trial, data interpretation and revised the manuscript critically. JA, BB, MKB, PB, EE, MG, FH, JK, RBvL, MK, PL, LJM, LS, RSp and MW were involved in data acquisition, and revised the manuscript critically. SH, MK, lvdL, PL, RSo and WdM were involved in planning and execution of the trial, and revised the manuscript critically. All authors approved the final version of the manuscript and agree to be accountable for all aspects of this trial. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. IAHvdb and MMNPK act as guarantors for the work and accept full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. JMP and JS shared last authorship.

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Online supplemental material

Van den Berk IAH, Kanglie MMNP, van Engelen TSR et al. OPTIMACT study group. Ultra-low-dose CT versus chest X-ray for patients suspected of pulmonary disease at the emergency department: a multicentre randomised clinical trial.

Table of contents	
	Members OPTIMACT study group.....2
Text S1	Radiation Dose calculation ULDCT and CXR.....7
Table S1	Excluded patients Amsterdam UMC and Spaarne Gasthuis.....8
Figure S1	Inclusions per month and per inclusion site.....9
Text S2	Availability of prior imaging.....10
Figure S2	The distribution of the Physical Component summary Scale (PCS) scores.....11
Text S3	Imputation and sensitivity analyses.....12
Table S2	Incidental findings: ULDCT versus CXR.....13
Table S3	Responders versus non-responders SF-12: baseline characteristics .....14
Table S4	Responders versus non-responders SF-12: symptoms and clinical question after initial evaluation at ED.....15
Table S5	Baseline characteristics complete.....16
Table S6	Diagnosis at ED discharge and Day 28 diagnosis complete.....17

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## Text S1 Radiation dose calculation ULDC and CXR

### Method

The effective dose of ULDC was calculated by multiplying the Dose Length Product (DLP) of the CT-acquisition with a dose conversion factor for the chest.<sup>1</sup> Calculation of the effective dose of the CXR were based on Monte Carlo simulations with PCXMC 2.0 (STUK, Helsinki, Finland). Input parameters for the simulations are the Dose area Product (DAP) of the acquisitions, source to patient distance, beam collimation, kVp and beam filtration.

### Result

The median ULDC dose was 0.2 mSv (IQR 0.2 to 0.3 mSv). The median CXR dose was for portable anterior posterior (AP) CXR 0.02 mSv (IQR 0.02 to 0.03 mSv) and bucky CXR posterior anterior (PA) and lateral 0.05 mSv (IQR 0.03 to 0.07 mSv).

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**Table S1** Excluded patients Amsterdam UMC and Spaarne Gasthuis (SG)

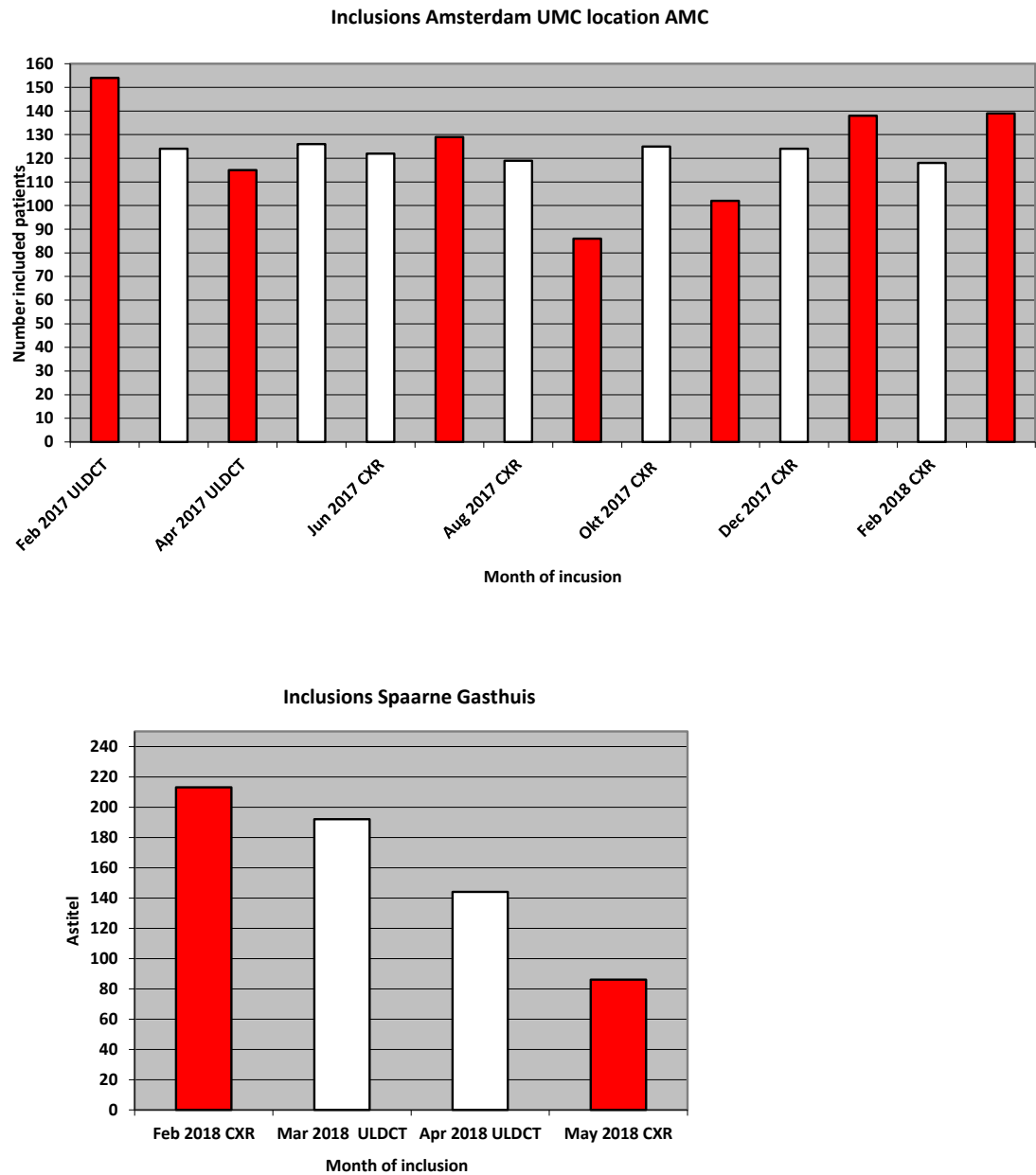
		Amsterdam UMC		Spaarne Gasthuis <sup>a</sup>	
Assessed for eligibility	Total (N=4807)	ULDCT (N=1887)	CXR (N=1981)	ULDCT (N=475)	CXR (N=464)
Randomised	2418	881	890	327	320
Excluded <sup>b</sup>	2389	1006	1091	148	144
Not meeting inclusion criteria	1286 (26.8)	611 (32.4)	617 (31.1)	19 (4.0)	39 (8.4)
Earlier participants	572	294	272	3	3
Barriers to follow-up data collection	232	85	130	7	10
Life expectancy less than one month	192	68	104	7	13
Incapacitated patients	178	84	80	2	12
Unable to undergo ULDCT or CXR	107	79	28	0	0
Pregnancy	5	1	3	0	1
Declined participation	237 (4.9)	119 (6.3)	115 (5.8)	2 (0.4)	1 (0.2)
Other reasons	866 (18.0)	276 (14.6)	359 (18.1)	127 (26.7)	104 (22.4)
Unknown	731	202	349	76	104
Transport problems	4	0	3	1	0
Waiting time too long	6	0	6	0	0
CT scanner not available	124	74	0	50	0
Electronic patient record error	1	0	1	0	0

ULDCT: Ultra-low-dose chest computed tomography, CXR: Chest X-ray.

<sup>a</sup> Due to privacy regulations the total number of patients assessed for eligibility, and the total number of patients excluded for randomization are incomplete. These numbers are composed of complete data (Amsterdam UMC, location AMC) and data from a random sample of non-included patients (Spaarne Gasthuis).

<sup>b</sup> Values are numbers (percentages).

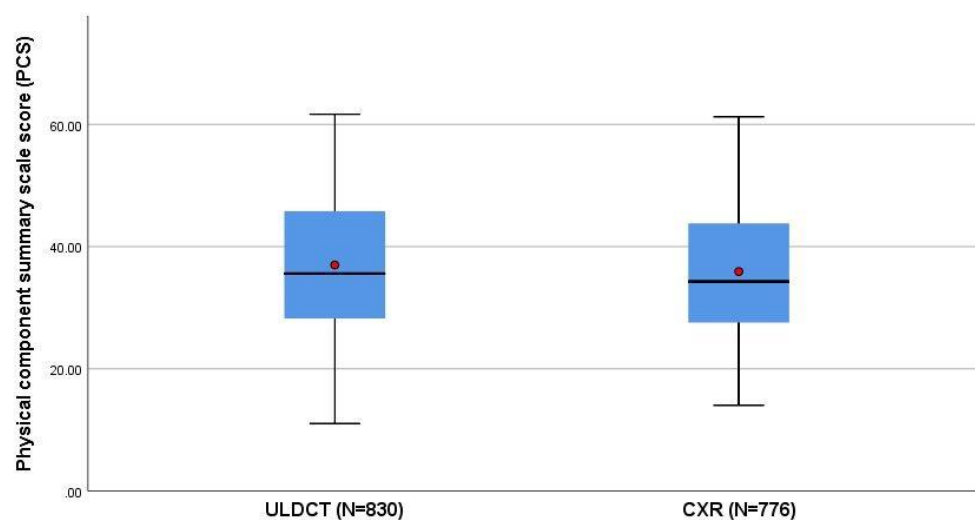




**Figure S1** Inclusions per month and per inclusion site. Red bars: ultra-low-dose chest computed tomography (ULDCT), White bars: chest X-ray (CXR)

**Text S2** Availability of prior imaging

The ULDCT and CXR were read with prior imaging if available. In the ULDCT group in 35.2% (425/1208) of patients a prior CXR was used during reading and in 31.7% (383/1208) a prior chest-CT. In the CXR group in 62.4% (788/1210) of patients a prior CXR was used during reading and in 11.9% (144/1210) a prior chest-CT. In patients in the CXR group, a prior CXR was more often used for comparison compared to the ULDCT group. This is in accordance with regular clinical practice and related to the two dimensional projection technique of CXR and the lower number of images.



**Figure S2** The distribution of the Physical component summary scale (PCS) scores.

ULDCT: Ultra-low-dose chest computed tomography, CXR: Chest X-ray

● Mean PCS score: ULDCT: 37.0 (95% CI 36.2 to 37.8), CXR: 35.9 (95% CI 35.2 to 36.7), difference 1.1 (95% lower CI: 0.003), histogram PCS in Supplement Figure S2.

### Text S3 Imputation and sensitivity analyses

#### Primary outcome: Sensitivity analyses

Sensitivity analysis including the imputed 109 PCS scores of incomplete questionnaires using age and sex as variables (excluding four questionnaires in the ULDCT group and one questionnaire in the CXR group that were sent back completely blank) showed a result similar to the primary analysis: mean PCS score 36.9 in the ULDCT group (n=892) versus 35.9 in the CXR group (n=823), a difference of 1.0 (one-sided 95% lower CI: -0.06). Non-inferiority of ULDCT to CXR within the prespecified 1-point margin was therefore shown in the non-imputed and imputed data. Multivariable linear regression analysis on the non-imputed data with imaging modality as a predictor as well as baseline characteristics (age, gender, comorbidity, presenting symptoms, clinical question on radiology application form) resulted in a mean difference in PCS scores of 0.9 (one-sided 95% lower CI: -0.1), also indicating non-inferiority of ULDCT.



**Table S2** Incidental findings: ULDCT versus CXR<sup>a</sup>

	<b>ULDCT (n= 1200)<sup>b</sup></b>	<b>CXR (n=1203)<sup>b</sup></b>	<b>Effect estimate (95% CI)</b>
<b>Incidental findings</b>	100 (8.3)	14 (1.2)	
Pulmonary nodules	54	7	
Pulmonary other	4	2	
Cardiovascular	19	3	
Upper abdomen	13	1	
Musculoskeletal	6	1	
Breast	3	0	
Neck	1	0	
Mediastinum	1	0	
<b>In follow-up because of incidental findings 28 days</b>	26 (2.2)	4 (0.3)	1.8 (1.0 to 2.7)
Pulmonary nodules	21	4	1.4 (0.6 to 2.2)
Pulmonary other	2	0	
Upper abdomen	3	0	

ULDCT: Ultra-low-dose chest computed tomography, CXR: Chest X-ray, CI: Confidence Interval.

<sup>a</sup> Values are numbers (percentages) unless otherwise specified.

<sup>b</sup> In imaging-per-protocol population.

**Table S3** Responders versus non-responders SF-12 questionnaire: baseline characteristics<sup>a</sup>

Characteristic	SF-12 returned (N=1720)	SF-12 not returned (N=698)	Standardized difference
Mean age (SD) <sup>b</sup> , y	59.8 (17.5)	56.9 (20.1)	0.2
Female sex	854 (49.7)	346 (49.6)	0.2
<b>Comorbidity</b>			
Charlson Comorbidity Index <sup>c</sup> (IQR)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	
Immunocompromised	392 (22.8)	139 (19.9)	7.2
Malignancy <sup>b</sup>	318 (18.5)	123 (17.6)	2.3
Diabetes <sup>b</sup>	320 (18.6)	155 (22.2)	8.9
Pulmonary disease			
Chronic obstructive pulmonary disease <sup>b</sup>	265 (15.4)	89 (12.8)	7.6
Asthma	180 (10.5)	70 (10.0)	1.4
Interstitial lung disease	42 (2.4)	15 (2.1)	2.0
Cystic fibrosis	22 (1.3)	6 (0.9)	4.1
Cardiac disease			
Myocardial infarction <sup>b</sup>	248 (14.4)	80 (11.5)	8.8
Chronic cardiac failure <sup>b</sup>	136 (7.9)	60 (8.6)	2.5
Neurological disease <sup>b</sup>	201 (11.7)	88 (12.6)	2.8
Kidney disease <sup>b</sup>	149 (8.7)	74 (10.6)	6.6
Thromboembolic disease	140 (8.1)	59 (8.5)	1.1

SD: standard deviation, IQR: interquartile range

<sup>a</sup> Values are numbers (percentages) unless otherwise specified.<sup>b</sup> Variables included in the Charlson Comorbidity Index<sup>c</sup> Charlson Comorbidity Index, excluding AIDS. Predicts 10-year survival in patients with multiple comorbidities

**Table S4** Responders versus non-responders SF-12 questionnaire: symptoms and clinical question after initial evaluation at Emergency Department<sup>a</sup>

Characteristic	SF-12 returned (N=1720)	SF-12 not returned (N=698)	Standardized difference
<b>Presenting symptoms</b>			
Dyspnoea	967 (56.2)	391 (56.0)	0.4
Cough	959 (55.8)	351 (50.3)	11.0
Fever	730 (42.4)	252 (36.1)	13.0
Thoracic pain	654 (38.0)	248 (35.5)	5.2
Sputum production	539 (31.3)	193 (27.7)	8.1
Haemoptysis	71 (4.1)	24 (3.4)	3.6
Confusion	57 (3.3)	34 (4.9)	7.9
<b>Clinical question on radiology request form</b>			
Pneumonia	1209 (70.3)	450 (64.5)	12.4
Pulmonary congestion	138 (8.0)	52 (7.4)	2.1
Bronchitis	120 (7.0)	45 (6.4)	2.1
Pneumothorax	60 (3.5)	45 (6.4)	13.6
Pleural effusion	46 (2.7)	35 (5.0)	12.2
Pulmonary tumour	15 (0.9)	5 (0.7)	1.8
Atelectasis	5 (0.3)	2 (0.3)	0.1
Pulmonary metastases	2 (0.1)	5 (0.7)	9.3
Other	125 (7.3)	44 (6.3)	3.8

SF-12: Short Form-12

<sup>a</sup> Values are numbers (percentages) unless otherwise specified.

**Table S5** Baseline characteristics complete<sup>a</sup>

Characteristics		ULDCT (n=1208)	CXR (n=1210)
Mean age (SD) <sup>b</sup> , y		59.0 (18.1)	59.0 (18.6)
Female sex		613 (50.7)	587 (48.5)
Comorbidity			
Charlson Comorbidity Index <sup>c</sup> (IQR)		3.0 (1.0-5.0)	3.0 (1.0-5.0)
Immunocompromised		285 (23.6)	246 (20.3)
Malignancy <sup>b</sup>		229 (19.0)	222 (18.3)
Solid tumour <sup>d</sup>	Total	151 (13)	168 (14.0)
	Localized	88 (7.3)	92 (7.6)
	Metastasized	63 (5.2)	76 (6.3)
Malignant lymphoma <sup>d</sup>		46 (3.8)	33 (2.7)
Leukemia <sup>d</sup>		32 (2.6)	21 (1.7)
Diabetes <sup>b</sup>		230 (19.0)	245 (20.2)
No end organ damage <sup>e</sup>		173 (14.3)	177 (14.6)
With end organ damage <sup>e</sup>		57 (4.7)	68 (5.6)
Pulmonary disease			
Chronic obstructive pulmonary disease <sup>c</sup>		175 (14.5)	179 (14.8)
Asthma		141 (11.7)	109 (9.0)
Interstitial lung disease		29 (2.4)	28 (2.3)
Cystic fibrosis		14 (1.2)	14 (1.2)
Cardiac disease			
Myocardial infarction <sup>b</sup>		159 (13.2)	169 (14.0)
Chronic cardiac failure <sup>b</sup>		98 (8.1)	98 (8.1)
Neurological disease <sup>b</sup>		140 (11.6)	149 (12.3)
Cerebrovascular disease <sup>b</sup>		128 (10.6)	133 (11.0)
Dementia <sup>b</sup>		8 (0.7)	7 (0.6)
Hemiplegia <sup>b</sup>		4 (0.3)	9 (0.7)
Kidney disease <sup>b</sup>		104 (8.6)	119 (9.8)
Thromboembolic disease		92 (7.6)	107 (8.8)
Peripheral vascular disease <sup>b</sup>		66 (5.5)	88 (7.3)
Liver disease		44 (3.6)	46 (3.8)
Cirrhosis		24 (2.0)	22 (1.8)
Chronic hepatitis		20 (1.7)	24 (2.0)

ULDCT: Ultra-low-dose chest computed tomography, CXR: Chest X-ray, IQR: interquartile range

<sup>a</sup> Values are numbers (percentages) unless otherwise specified.

<sup>b</sup> Variables included in the Charlson Comorbidity Index

<sup>c</sup> Charlson Comorbidity Index, excluding AIDS. Predicts 10-year survival in patients with multiple comorbidities

<sup>d</sup> Within the past 5 years, except for chronic lymphatic leukaemia

<sup>e</sup> End organ damage: retinopathy, neuropathy, or nephropathy



**Table S6** Diagnosis at ED discharge and Day 28 diagnosis complete<sup>a b</sup>

Day 28 diagnosis	ULDCT (n=1161)		CXR (n=1151)	
	Diagnosis at ED discharge	Diagnosis at Day 28	Diagnosis at ED discharge	Diagnosis at Day 28
Extra-thoracic pathology	259 (22.3)	299 (25.8)	246 (21.4)	338 (29.4)
Community-acquired pneumonia	255 (22.0)	225 (19.4)	189 (16.4)	169 (14.7)
Thoracic pain of unknown origin	110 (9.5)	122 (10.5)	112 (9.7)	135 (11.7)
Fever of unknown origin	111 (9.6)	53 (4.6)	85 (7.4)	46 (4.0)
Lower respiratory tract infection other than pneumonia	101 (8.7)	121 (10.4)	100 (8.7)	116 (10.1)
COPD exacerbation	83 (7.1)	116 (10.0)	72 (6.3)	127 (11.0)
No definite diagnosis yet	78 (6.7)	-	108 (9.4)	-
Congestive heart failure	66 (5.7)	66 (5.7)	87 (7.6)	110 (9.6)
(Possible) influenza A/B <sup>c</sup>	53 (4.6)	96 (8.3)	22 (1.9)	73 (6.3)
Other thoracic pathology	57 (4.9)	60 (5.2)	66 (5.7)	63 (5.5)
Asthma exacerbation	51 (4.4)	75 (6.5)	34 (3.0)	49 (4.3)
Upper respiratory tract infection	49 (4.2)	52 (4.5)	48 (4.2)	64 (5.6)
Healthcare-associated pneumonia	4 (0.3)	50 (4.3)	8 (0.7)	37 (3.2)
Dyspnoea of unknown origin	32 (2.8)	26 (2.2)	48 (4.2)	23 (2.0)
Cardiac arrhythmia	32 (2.8)	34 (2.9)	34 (3.0)	36 (3.1)
Pleural effusion or empyema	22 (1.9)	27 (2.3)	12 (1.0)	33(2.9)
No pathology	22 (1.9)	21 (1.8)	30 (2.6)	20 (1.7)
Stable angina pectoris	16 (1.4)	17 (1.5)	13 (1.1)	7 (0.6)
Pulmonary embolism	14 (1.2)	18 (1.6)	29 (2.5)	28 (2.4)
Lung cancer or pulmonary metastases	8 (0.7)	19 (1.6)	8 (0.7)	21 (1.8)
Pericarditis	11 (0.9)	11 (0.9)	9 (0.8)	13 (1.1)
ACS with troponin	6 (0.5)	3 ( 0.3)	16 (1.4)	16 (1.4)
Interstitial lung disease	6 (0.5)	13 (1.1)	1 (0.1)	6 (0.5)
Sinusitis	9 (0.8)	11 (0.9)	9 (0.8)	9 (0.8)
Exacerbation CF	7 (0.6)	9 (0.8)	9 (0.8)	10 (0.9)
Pneumothorax	7 (0.6)	7 (0.6)	7 (0.6)	6 (0.5)
ACS without troponin	6 (0.5)	6 (0.5)	7 (0.6)	6 (0.5)
Aspiration pneumonia	8 (0.7)	6 (0.5)	5 (0.4)	4 (0.3)
Atelectasis	5 (0.4)	1 (0.09)	1 (0.1)	1 (0.09)
Pleuritis sicca	3 (0.3)	0 (0.0)	2 (0.2)	1 (0.09)
Mediastinal tumour	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.09)
Acute chest syndrome	1 (0.1)	1 (0.09)	2 (0.2)	2 (0.2)
Radiation pneumonia	0 (0.0)	1 (0.09)	1 (0.1)	1 (0.09)

ULDCT: Ultra-low-dose chest computed tomography, CXR: Chest X-ray, COPD: Chronic obstructive pulmonary disease, CF: Cystic fibrosis, ACS: acute coronary syndrome

<sup>a</sup> Values are numbers (percentages).

<sup>b</sup> Patients could have more than one diagnosis.

<sup>c</sup> (Possible) influenza A/ B: at ED discharge a diagnosis of possible influenza A/B was assigned if a patient was treated for influenza A/B awaiting the results of the PCR test. At day 28 a diagnosis of influenza A/B was assigned to PCR positive patients accordingly.