Diagnostic Performance of Chest CT for SARS-CoV-2 Infection in Individuals with or without COVID-19 Symptoms

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Key Results:

• CT with structured CO-RADS scoring has good diagnostic performance for COVID-19 pneumonia in both symptomatic (AUC=0.89) and asymptomatic (AUC=0.70) individuals (P<0.001).

• In symptomatic individuals (42% PCR+), CO-RADS ≥ 3 detected positive PCR with acceptable sensitivity (89%) and specificity (73%) resulting in PPV of 70%.

• In asymptomatic individuals (5% PCR+), CO-RADS ≥ 3 detected SARS-CoV-2 infection with low sensitivity (45%) but high specificity (89%) and PPV of 18%.

Summary Statement:

Categorization of COVID-19 suspicion by CO-RADS CT has good diagnostic performance in individuals with or without symptoms. While CT screening for asymptomatic SARS-CoV-2 infections is not recommended, incidental findings of CO-RADS ≥ 3 in asymptomatic individuals have sufficient positive predictive value to trigger SARS-CoV-2 PCR reflex testing.

Abbreviations:

CORADS: COVID-19 Reporting and Data System; COVID-19: Coronavirus disease 2019; LR: likelihood ratio; RT-PCR: reverse transcription polymerase chain reaction

Abstract

Background: The use of chest CT for COVID-19 diagnosis or triage in healthcare settings with limited SARS-CoV-2 PCR capacity is controversial. CO-RADS categorization of the level of COVID-19 suspicion might improve diagnostic performance.

Purpose: To investigate the value of chest CT with CO-RADS classification to screen for asymptomatic SARS-CoV-2 infections and to determine its diagnostic performance in individuals with COVID-19 symptoms during the exponential phase of viral spread.

Materials and Methods: In this secondary analysis of a prospective trial (Clinical Trial Number: IRB B1172020000008), from March 2020 to April 2020, we performed parallel SARS-CoV-2 PCR and CT with categorization of COVID-19 suspicion by CO-RADS, for individuals with COVID-19 symptoms and controls without COVID-19 symptoms admitted to the hospital for medical urgencies unrelated to COVID-19. CT-CORADS was categorized on a 5-point scale from 1 (very low suspicion) to 5 (very high suspicion). AUC were calculated in symptomatic versus asymptomatic individuals to predict positive SARS-CoV-2 positive PCR and likelihood ratios for each CO-RADS score were used for rational selection of diagnostic thresholds.

Results: 859 individuals (median 70 years, IQR 52-81, 443 men) with COVID-19 symptoms and 1138 controls (median 68 years, IQR 52-81, 588 men) were evaluated. CT-CORADS had good diagnostic performance (P<.001) in both symptomatic (AUC=.89) and asymptomatic (AUC=.70) individuals. In symptomatic individuals (41.7% PCR+), CO-RADS ≥ 3 detected positive PCR with high sensitivity (89%, 319/358) and 73% specificity. In asymptomatic individuals (5.3% PCR+), a CO-RADS score ≥ 3 detected SARS-CoV-2 infection with low sensitivity (45%, 27/60) but high specificity (89%).

Conclusion: CT-CORADS had good diagnostic performance in symptomatic individuals, supporting its application for triage. Sensitivity in asymptomatic individuals was insufficient to justify its use as first-line screening approach. Incidental detection of CO-RADS $\geq$ 3 in asymptomatic individuals should trigger testing for respiratory pathogens.

Introduction

Chest CT can help determine the temporal disease stage and severity of COVID-19 pneumonia [1-3]. In the early stage of viral replication (day 0-4) ground-glass opacities are the predominant lesion. In the progressive stage (day 5-8), crazy paving patterns mark the increased recruitment of inflammatory cells to the lung interstitium. Peak stage (day 10-13) is marked by consolidation with fibrosis and diffuse alveolar damage. These radiological lesions are also observed in other viral pneumonia and non-infectious inflammatory lung diseases but in a pandemic context might harbor diagnostic potential for SARS-CoV-2 infection especially for patient triage. The reference method for COVID-19 diagnosis, SARS-CoV-2 PCR, is highly specific but has variable sensitivity as low as 70% [4]. In health care settings with limited PCR capacity and long turnaround times, chest CT was proposed as alternative for COVID-19 diagnosis or triage [5]. Studies supporting chest CT as first-line diagnostic tool for COVID-19 showed several methodological concerns [6-8]. Most studies were underpowered, showed major selection biases including only individuals with COVID-19 symptoms and 40%-50% a priori risk of SARS-CoV-2 infection and used binary scoring of CT without standardized definition of COVID-19-compatible CT. Weighed against the cost and procedural risks of CT, this sparked a controversy [8][9] leading to consensus statements by the Centers for Disease Control and Prevention, the American College of Radiology, the Society of Thoracic Radiology, the American Society of Emergency Radiology, The Fleischner Society, and the Radiological Society of North America (RSNA), opposing CT as first-line COVID-19 diagnostic tool [10-13].

In this report, we studied the diagnostic power of chest CT versus SARS-CoV-2 PCR using COVID-19 Reporting and Data System classification system (CO-RADS) [14]. CO-RADS was developed by the Dutch Radiological Society to categorize the level of suspicion for COVID-19 pneumonia. It generally aligns with the structured reporting recommended by the RNSA [13], scoring the level of COVID-19 suspicion on a scale of 1 to 5, with CO-RADS 1 corresponding to 'negative' category, CO-RADS 2 to 'Atypical', CO-RADS 3 and 4 corresponding to 'Indeterminate' with 'lower' or 'higher likelihood', and CO-RADS 5 equaling the RNSA 'Typical' category.

The purpose of this study was to investigate the value of chest CT with CO-RADS classification to screen for asymptomatic SARS-CoV-2 infections and to determine its diagnostic performance in individuals with COVID-19 symptoms during the exponential phase of viral spread. These data should allow a more evidence-based definition of the possible role of chest CT in COVID-19 triage.

Materials and Methods

Participants   This is a secondary analysis of a single-center prospective trial on consecutive individuals admitted to AZ Delta General Hospital in Roeselare, Belgium from March 19, 2020 to April 20, 2020. AZ Delta General Hospital is a central-network regional hospital that provides tertiary healthcare for a community of 500,000 inhabitants. Inclusion criteria: as part of the medical board-approved triage policy for COVID-19 quarantining, all individuals admitted to the hospital with clinical suspicion of COVID-19 pneumonia (hence 'symptomatic individuals') and individuals without COVID-19 symptoms but admitted for other medical urgencies, scheduled surgery or medical procedures and psychiatric or geriatric care (hence 'asymptomatic individuals'), received a combined screening with chest CT and SARS-CoV-2 PCR within a 24-hour time frame. We used the COVID-19 case definition as specified by the World Health Organization (WHO) interim guidance of February 27, 2020 [15] for classifying symptomatic individuals. Exclusion criteria: children < 14 years of age and pregnant individuals without COVID-19 symptoms did not receive standard chest CT. The study was approved by the AZ Delta Institutional Review Board with a waiver of written informed consent from study participants considering the study is based on secondary analysis of existing data (Clinical Trial Number: IRB B1172020000008, study protocol available through the registry of the Belgian Advisory Committee on Bioethics and email request to corresponding author). Authors received no specific funding for this study.

CT protocol Within 24h from admission all individuals were imaged by multi-detector CT using either GE LightSpeed VCT scanner (1-mm slice thickness), Siemens Somatom AS (1-mm slice thickness) or

the GE Optmima 660 scanner (1.25-mm slice thickness). All scans were performed without

intravenous contrast with the patient in the supine position during end-inspiration.

Image evaluation Two cardiothoracic radiologists with 24 and 9 years of experience (Gryspeerdt S.,

De Smet K.) retrospectively reviewed the CT exams on a PACS workstation (IDS7, Sectra) with

multiplanar reconstruction tools. Reviewers were blinded to (a)symptomatic status and PCR result.

Final CO-RADS scoring was always reached by consensus. The Dutch CO-RADS (COVID-19 Reporting

and Data System) classification system was used to categorize the level of COVID-19 suspicion,

exactly as described [14] : CO-RADS score ranges from 1 (very low level of suspicion), 2 (low level), 3

(equivocal), 4 (high level of suspicion) to 5 (very high level of suspicion) (summarized and

representative images in Fig. 3). See Appendix E1 for detailed CT protocol.

Comorbidities were recorded by chest CT (chronic lung disease including emphysema, fibrosis and

bronchiectasis and coronary artery disease as derived from coronary artery calcification scoring) or

review of medical records (diabetes).

SARS-CoV-2 PCR was done with multiplex RT-PCR (hence PCR) for E/N/RdRP genes using Allplex™

2019-nCoV assay (Seegene Inc, Seoul, Korea) on nasopharyngeal swabs.

Statistical analysis

The diagnostic performance of categorical CT-assessment by CO-RADS classification (CT-CORADS)

was evaluated by calculating area (AUC) under the receiver operating characteristics (ROC) curve

compared to SARS-CoV-2 PCR positivity. Likelihood ratios (LR, 95%CI) were calculated for each CO-

RADS score in the symptomatic versus the asymptomatic group and visualized in diagrams of

pre/post-test probability. According to Bayes' theorem, post-test probability (P_{post}) can be derived

from pre-test probability (P_{pre}) and LR according to the formula $P_{post} = (P_{pre} \times LR) / (1 + P_{pre} \times (LR-1))$

where P_{pre} represents the prevalence of SARS-CoV-2 PCR-positivity in any population under study.

Statistical differences in demographics and comorbidities were evaluated by Mann-Whitney test

(age) and Chi-squared test (proportions). Statistical analyses were performed using MedCalc (version

12.2.1, MedCalc Software, Mariakerke, Belgium) and considered significant if P value was less than

.05.

Results

Participant Characteristics

A total of 1997 consecutive individuals (flowchart Fig. 1) admitted to the hospital were allocated by

physical examination and anamnesis into two groups. First, 859 individuals were admitted with

WHO-listed symptoms of COVID-19 pneumonia (hence 'symptomatic individuals'): 443 males

(median age 71 years, IQR 54-80 years) and 416 females (median age 68 years, IQR 51-82 years)

(Table 1). Second, 1138 individuals were admitted for medical needs unrelated to WHO-listed COVID-

19 symptoms (hence 'asymptomatic individuals'): 588 males (median age 66 years, IQR 53-78 years)

and 550 females (median age 70 years, IQR 50-82 years). Demographics and key clinical

comorbidities are shown in Table 1: individuals with or without COVID-19 symptoms showed a

similar age- and sex-distribution and a similar prevalence of diabetes and coronary artery disease

(Table 1). PCR-negative symptomatic individuals had higher rates of underlying chronic lung disease

(27.9%, 140 of 501) than PCR-positive symptomatic (21.5%, 77 of 358, P<0.05) and PCR-negative

asymptomatic individuals (20.6%, 222 of 1078, P<0.05).

Diagnostic performance in symptomatic individuals

The overall prevalence of SARS-CoV-2 infection in symptomatic individuals was 41.7% (358 of 859). In

symptomatic individuals with CO-RADS 5, 89.4% (279 of 312) were PCR+ as compared to only 8.6%

(27 of 313) PCR+ cases in symptomatic individuals with CO-RADS 1. ROC analysis confirmed the

diagnostic performance (P<0.001) of CT-CORADS with AUC = .89 (95%CI .87-.91) to predict SARS-

CoV-2 PCR-positivity (Fig. 2A). Next we calculated likelihood ratios (LR) for each CO-RADS score in symptomatic individuals (Table 2): CORADS 1, 2 and also the 'equivocal' score CORADS 3 (LR=0.34, 95%CI 0.20-0.59) significantly lowered the odds of PCR positivity (confidence interval of LR excluding LR=1). CO-RADS 4 did not further increase post-test probability. CO-RADS 5, however, strongly increased the odds of a positive PCR (LR=11.8 95%CI 8.5-16.5) (Fig. 2B). A CO-RADS 5 score in symptomatic individuals identified SARS-CoV-2 PCR positivity with a sensitivity of 77.9% (95%CI 73.3-82.1) at high specificity of 93.4% (95%CI 90.9-95.4) and high overall accuracy of 87.0% (95%CI 84.5-89.1). Dichotomization of suspected CT at CO-RADS ≥ 4 and ≥ 3 increased sensitivity to 84.3% (95%CI 80.8-88.5) and 89.1% (95%CI 85.4-92.1) at a specificity of 84.8% (95%CI 68.3-76.3) and 72.5% (95%CI 68.3-76.3) respectively (Table 2). Table 2 and Fig.2B show the associated shift from pre-test probability (overall prevalence of positive PCR) to post-test probability (positive predictive value) of SARS-CoV-2 as function of individual CO-RADS scores or dichotomizations.

Screening potential of chest-CT in asymptomatic individuals in a SARS-CoV-2 pandemic setting. The prevalence of SARS-CoV-2 PCR-positivity (pre-test probability), in asymptomatic individuals was 5.3% (60 of 1138). 6.9% (79 of 1138) of asymptomatic individuals showed a CO-RADS score of 4 (high suspicion) or 5 (very high suspicion), 87.0% (990 of 1138) showed a CO-RADS score ≤ 2 with low to very low suspicion of COVID-19 (Table 2). ROC analysis indicated that CT-CORADS in asymptomatic individuals had diagnostic performance (P<0.001) to predict SARS-CoV-2 PCR-positivity with AUC = .70 (95%CI .67-.73) (Fig. 2A), albeit less than in symptomatic individuals. The percentage of PCR-positive cases was 3.0%, 8.2%, 11.6%, 17.8% and 32.4% in CO-RADS 1, 2, 3, 4 and 5, respectively. Analysis of LR (Table 2, Fig. 2C) indicated that only CO-RADS 1 could significantly lower the odds of a positive PCR (LR=0.56, 95%CI 0.43-0.73), that CO-RADS 2 had no diagnostic meaning with the 95% CI encompassing LR=1 and that CO-RADS 3 and higher, chest CT increased the odds of a positive PCR, resulting in a positive shift from pre- to post-test probability (Fig. 2C). In particular CO-RADS 5 had good diagnostic performance in asymptomatic individuals, with LR =8.6 (95%CI 4.4-17), predicting

SARS-CoV-2 infection at high specificity of 97.9% (95%CI 96.8-98.6) but low sensitivity of 18.3% (95%CI 9.5-30). Dichotomization of suspected CT at CO-RADS ≥ 4 preserved a high specificity of 94.4% (95%CI 93-96) resulting in a post-test probability (positive predictive value) of 24.1% (95% CI 20-28) (Table 2, Fig. 2C). Its sensitivity was low at 31.7% (95%CI 20-45) resulting in a negligible shift in pre- to post-test probability in case of a negative test result (3.9%, 95% CI 3.2-4.2), arguing against the use of chest CT as a screening test for asymptomatic infections.

Representative clinical images. A summary of the CO-RADS scoring system and representative CT images for CO-RADS 1 to 5 are shown in Fig. 3. Fig. 4 to 6 highlight individual cases with a brief clinical summary of: (i) a false positive CO-RADS 5 in a PCR-negative symptomatic individual (Fig. 4), (ii) false negative CO-RADS 1 in a PCR-positive symptomatic individual (Fig. 5) and (iii) true positive CO-RADS 5 in a PCR-positive asymptomatic individual.

Discussion

We aimed to investigate the performance of CT-CORADS to diagnose SARS-CoV-2 PCR-positivity in individuals with COVID-19 symptoms and to screen for asymptomatic SARS-CoV-2 infection in control individuals in a setting with high prevalence of SARS-CoV-2 infections. In symptomatic patients, the pre-test probability of SARS-CoV-2 infection, as marked by the prevalence of PCR-positivity, was high at 41.7%. A CO-RADS score ≥ 3 strongly increased post-test probability to 69.8% and CO-RADS 5 even to 89.4%. For infection control policies, CO-RADS 5 could thus be used as triage tool to quarantine symptomatic individuals in settings with bottlenecks in PCR testing. Yet, CO-RADS < 3 was still associated with a post-test probability of 9.7% (corresponding to a 90.3% negative predictive value) indicating that chest CT cannot replace PCR as diagnostic test. In our asymptomatic controls, prevalence of SARS-CoV-2 PCR-positivity was 5.3%, in line with the secondary attack rate at population level of 6.6% during the exponential phase of viral spread [16]. This control group was thus suitable to investigate if chest CT can screen for asymptomatic SARS-CoV-2 infection. Also in

asymptomatic individuals CT-CORADS showed good diagnostic performance. However, various

dichotomization scenarios failed to reach the high sensitivity required for a screening test. CO-RADS

≥ 4 attained only 31.7% sensitivity. A negative test (CO-RADS <4) shifted pre- to post-test probability

only from 5.3% to 3.9%, insufficient to justify the procedural risk of CT. The specificity of CO-RADS ≥

4 in asymptomatic individuals, however, was high (94.4%) and resulted in meaningful increase in

post-test probability to 24.1%. In a pandemic setting, we propose that such incidental findings should

be reported as 'compatible with COVID-19 pneumonia' rather than as 'viral pneumonia' as suggested

by the RNSA [13] and should trigger SARS-CoV-2 PCR or syndromic panel-based PCR testing for other

respiratory pathogens before exclusion of non-infectious inflammatory lung diseases.

The developers of CO-RADS reported a good diagnostic performance in a pilot study on 105

individuals with COVID-19 symptoms and 50.5% PCR-positivity with AUC under the ROC curve of 0.91

(95% CI 0.85-0.97) [14]. Our study confirms this with similar AUC on a much larger sample. As

compared with previous studies supporting chest CT for COVID-19 diagnosis or screening [3,17,18,19], our

study answered the urgent call for well-powered data sets [18] and its prospective design on

consecutive, unselected individuals with similar demographics, comorbidities and upfront clinical

grouping according to absence or presence of COVID-19 symptoms, minimizes selection biases.

Another strength is the use of structured reporting of chest CT data and the attribution of likelihood

ratios (LR) to each level of suspicion.   Most studies thus far used dichotomization of CT results as

positive or negative, often without a clear definition of a positive CT. One large study in China

reported a 97% sensitivity of chest CT for COVID-19 diagnosis but with a poor specificity of 25% [3],

possibly explained by a low subjective interpretation threshold to maximize sensitivity [19].

Like sensitivity and specificity, LR are test properties that, in defined patient populations, are

independent of disease prevalence. The actual clinical values of a positive test result to confirm or

negative test result to rule-out disease, the positive (PPV) and negative (NPV) predictive value

respectively, strongly depend on disease prevalence [19]. Using LR, the post-test probability as

indicator of PPV can simply be calculated (formula in Methods) taking the observed prevalence of

PCR-positivity as pre-test probability. Similarly, NPV is 1 minus the post-test probability. PPV is mathematically most influenced by specificity [19]. Meta-analysis showed a low pooled specificity of dichotomic chest CT of 37% for COVID-19 diagnosis [20] with low associated PPV from 1.5%-8.3% in low prevalence (<10%) settings. Our data illustrate that CO-RADS categorization improves specificity and thus discloses higher PPV as LR increase. NPV is mostly influenced by sensitivity [19]. In our data set, sensitivity of chest CT was insufficient to exclude SARS-CoV-2 infection both in symptomatic and asymptomatic patients. This supports the consensus statements that chest CT should not be used as diagnostic test.

Our study has limitations. It was conducted in a time frame with high rates of SARS-CoV-2 infections and low prevalence of other viral pneumonia. Higher incidence of seasonal respiratory viral infections will likely decrease specificity of CT-CORADS. Selection bias: study included mostly individuals older than 50 years attending the hospital and excluded pediatric and pregnant individuals. Paucisymptomatic infections in home-quarantined older individuals and asymptomatic infections in younger individuals are underrepresented in our data set.

In conclusion, our data show that CT with structured CO-RADS scoring had good diagnostic performance for COVID-19 pneumonia but cannot replace SARS-CoV-2 PCR as diagnostic test. It can be used as alternative triage tool in individuals with COVID-19 symptoms but not for the screening of asymptomatic SARS-CoV-2 infections.

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Tables

Table 1. Demographics and Key Clinical Data of Study Participants

Participant group	Characteristics	PCR (+)	PCR (-)	*P*
Symptomatic individuals (n = 859)				
	n	358	501	
	Sex			
	Female, n (%)	165 (46)	251 (50)	.28
	Male, n (%)	193 (54)	250 (50)	
	Age, Median (IQR), y	68 (53-80)	71 (52-81)	.84
	Chronic lung disease, n (%)	77 (212)	140 (28) [†]	.04
	Coronary artery disease, n (%)	194 (54)	281 (56)	.63
	Diabetes, n (%)	48 (13)	60 (12)	.61
Asymptomatic individuals (n = 1178)				
	n	60	1078	
	Sex			
	Female, n (%)	28 (47)	522 (48)	.90
	Male, n (%)	32 (53)	556 (52)	
	Age, Median (IQR), y	73 (51-82)	68 (52-80)	.65
	Chronic lung disease, n (%)	11 (18)	222 (21) [†]	.79
	Coronary artery disease, n (%)	34 (57)	564 (52)	.60
	Diabetes, n (%)	5 (8)	136 (13)	.43

P values less than .05 were considered statistically significant.
[†] Additional symptomatic to asymptomatic subgroup comparisons for prevalence of comorbidities for which
P values less than.05 were considered statistically significant.
PCR: reverse transcription Polymerase Chain Reaction

Table 1 lists the number of participants, sex distribution (number, %), median age (IQR) for

participants with COVID-19 symptoms (Symptomatic individuals) and individuals admitted for non-

COVID-19 indications (Asymptomatic individuals) and grouped according to their positive (PCR(+)) or

negative (PCR(-)) SARS-CoV-2 test result. For each group, key co-morbidities were listed as recorded

by chest CT (Chronic lung disease, Coronary artery disease) or review of medical records (Diabetes).

Table 2. Diagnostic Performance of CO-RADS for Symptomatic and Asymptomatic Setting at Different CO-RADS Cut-offs and Multiple Result Intervals.

CO-RADS cut-off	PCR(+)	PCR(-)	LR (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Post-test probability,% (95% CI)
						Pre-test probability = 41.7%
Symptomatic individuals (n = 859)	358	501				
CO-RADS ≥ 3						
CO-RADS 1-2	39	363	0.15 (0.11 - 0.20)	89 (85 - 92)	73 (68 -76)	9.7 (7.3 - 13)
CO-RADS 3-5	319	138	3.2 (2.8 - 3.8)			70 (67 - 73)
CO-RADS ≥ 4						
CO-RADS 1-3	54	425	0.18 (0.14 - 0.23)	85 (81 - 89)	85 (68 - 76)	11 (9.1 - 14)
CO-RADS 4-5	304	76	5.6 (4.5 - 6.9)			80 (76 - 83)
CO-RADS ≥ 5						
CO-RADS 1-4	79	468	0.24 (0.19 - 0.29)	78 (73 - 82)	93 (91 - 95)	15 (12 - 17)
CO-RADS 5	279	33	12 (8.5 - 17)			89 (86 - 92)
Multiple results intervals						
CO-RADS 1	27	286	0.13 (0.09 - 0.19)			8.5 (6.0 - 12)
CO-RADS 2	12	77	0.22 (0.12 - 0.40)			14 (7.9 - 22)
CO-RADS 3	15	62	0.34 (0.20 - 0.59)			20 (13 - 30)
CO-RADS 4	25	43	0.81 (0.51 - 1.3)			37 (27 - 48)
CO-RADS 5	279	33	12 (8.5 - 16)			89 (86 - 92)
						Pre-test probability = 5.3%
Asymptomatic individuals (n = 1138)	60	1078				
CO-RADS ≥ 3						
CO-RADS 1-2	33	957	0.62 (0.49 - 0.78)	45 (32 - 58)	89 (87 - 91)	3.3 (2.7 - 4.2)
CO-RADS 3-5	27	121	4.0 (2.9 - 5.6)			18 (14 - 24)
CO-RADS ≥ 4						
CO-RADS 1-3	41	1018	0.72 (0.61 - 0.86)	32 (20 - 45)	95 (93 - 96)	3.9 (3.2 - 4.2)
CO-RADS 4-5	19	60	5.6 (4.5 - 6.9)			24 (20 - 28)
CO-RADS ≥ 5						
CO-RADS 1-4	49	1055	0.83 (0.74 - 0.94)	18 (9.5 - 30)	98 (97 - 99)	4.4 (4.0 - 5.0)
CO-RADS 5	11	23	8.6 (4.4 - 17)			32 (20 - 48)
Multiple results intervals						
CO-RADS 1	28	901	0.56 (0.43 - 0.73)			3.0 (2.3 - 3.9)
CO-RADS 2	5	56	1.6 (0.67 - 3.9)			8.2 (3.6 -18)
CO-RADS 3	8	61	2.4 (1.2 - 4.7)			11 (6.2 – 21)
CO-RADS 4	8	37	3.9 (1.9 – 8.0)			18 (9.5 - 31)
CO-RADS 5	11	23	8.6 (4.4 - 17)			32 (20- 48)

CI, confidence interval; CO-RADS, COVID-19 Reporting and Data System classification system; LR, likelihood ratio; Sn, sensitivity; Sp, specificity; PCR: reverse phase Polymerase Chain Reaction Ppre, pre-test probability (= prevalence of positive PCR); Ppost, post-test probability

Table 2 shows the distribution of asymptomatic and symptomatic individuals over multiple result intervals (CO-RADS score 1 to 5) and various possible dichotomization approaches, with their associated number of positive/negative PCR tests and the associated likelihood ratios (LR, 95% confidence interval) to predict positive PCR. The sensitivity (Sn) specificity (Sp) with 95% confidence

intervals are calculated for various test dichotomizations. The right column indicates the post-test

probability of SARS-CoV-2 PCR positivity as indicator of positive and negative predictive value,

calculated according to the formula in Methods taking the measured prevalence of PCR-positivity in

either group as pre-test probability.

Figure Legends

All consecutive individuals admitted from March 19, 2020 to April 20, 2020 (N=1997)
Inclusion: all medical urgencies, pre-operative/pre-procedural, scheduled psychiatric and geriatric admissions
Exclusion: pediatric and pregnant individuals

Anamnesis and physical examination

Individuals with WHO-listed COVID-19 symptoms
admitted for clinical suspicion of COVID-19 pneumonia
"Symptomatic individuals" (N=859)

Individuals without WHO-listed COVID-19 symptoms
admitted for COVID-19-unrelated medical need
"Asymptomatic individuals" (N=1138)

Combined analysis within 24h of:
- **PCR** SARS-CoV-2 E/N/RdRP on nasopharyngeal swab
- **Chest CT with CO-RADS** classification of COVID-19 suspicion
- **Comorbidities**: COPD, coronary artery diseases, diabetes

PCR(+)
N=358 (42%)
Disease positive

PCR(-)
N=501 (58%)
Disease negative

PCR(+)
N=60 (5%)
Disease positive

PCR(-)
N=1078 (95%)
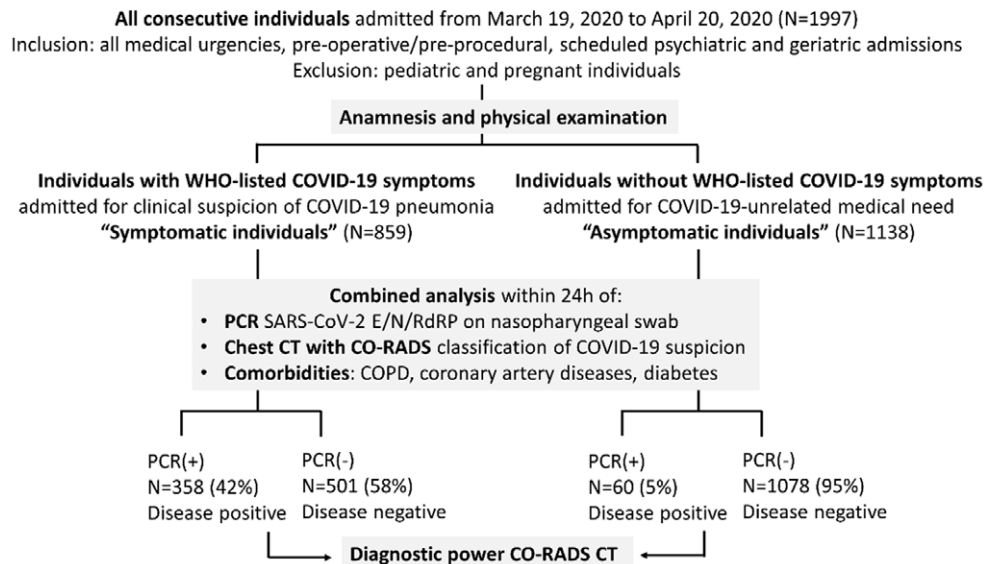Disease negative

Diagnostic power CO-RADS CT

Figure 1: Flow diagram of study. Abbreviations: COVID-19 Reporting and Data System classification system; PCR: reverse phase Polymerase Chain Reaction test for SARS-CoV-2 viral RNA sequences E/N/RdRP; WHO: World Health Organization.
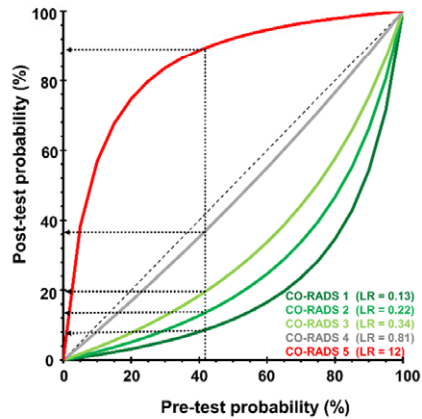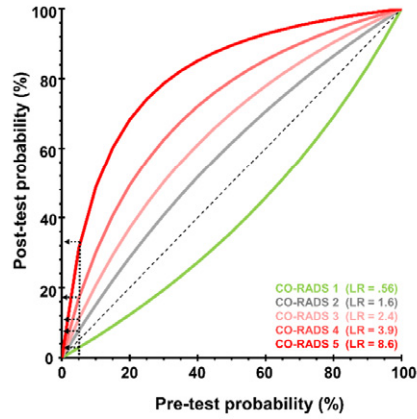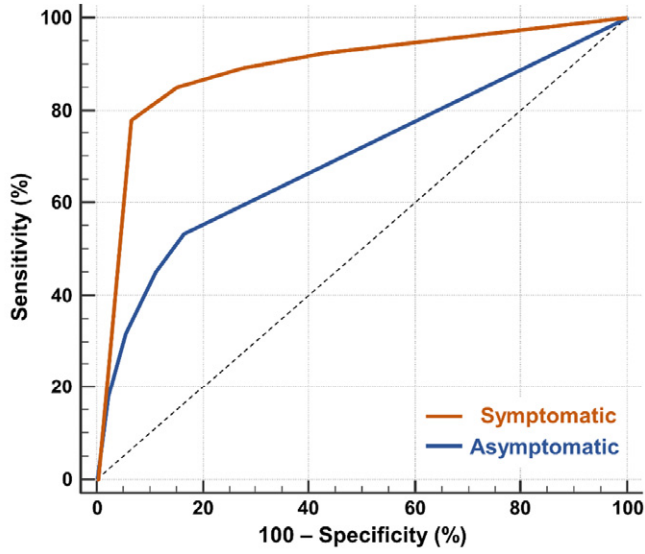
Figure 2: Diagnostic performance of CT-CORADS scoring in individuals with and without COVID-19 symptoms. *A,* The area under the receiver operating characteristics curve (AUC) of CT-CORADS to predict a positive SARS-CoV-2 PCR result in symptomatic (red line) and

asymptomatic (blue line). The diagonal dashed line indicates no discrimination. *B,* Post-test probability of positive PCR as function of the pre-test probability for different likelihood ratios (LR) associated with the indicated CO-RADS score in 859 symptomatic individuals. The arrow indicates the pre-test probability as determined by overall prevalence of positive PCR (41.7%) in this sample. *C,* Post-test probability of positive PCR as function of the pre-test probability for different likelihood ratios (LR) associated with the indicated CO-RADS score in 1138 asymptomatic individuals. The arrow indicates the pre-test probability as determined by overall prevalence of positive PCR (5.2%) in this sample.
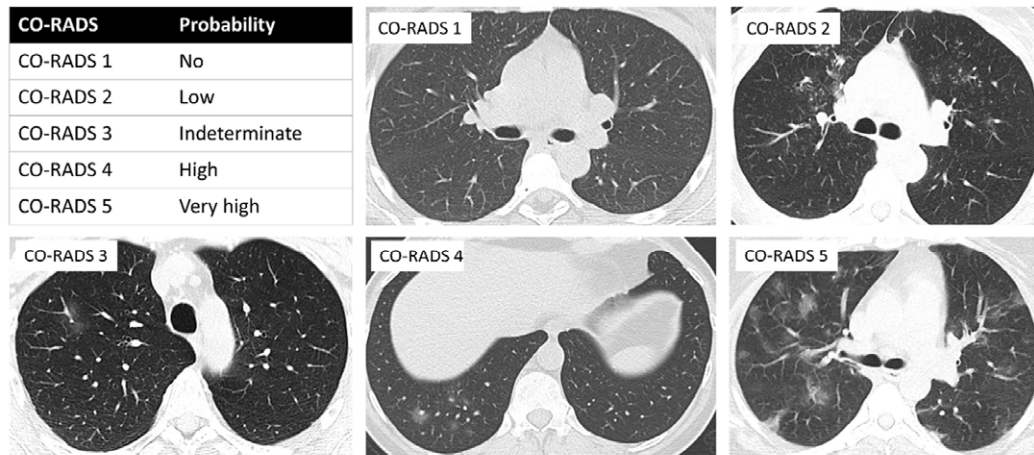

Figure 3: Illustration of CO-RADS scoring system for level of COVID-19 pneumonia suspicion. COVID-19 Reporting and Data System classification system (CO-RADS) scores the level of COVID-19 pneumonia suspicion as summarized in the upper left panel. The other panels show representative scans for CO-RADS 1 (no suspicion: normal findings), CO-RADS 2 (low level of suspicion: absence of ground glass opacities (GGO), presence of tree-in-bud signs/endobronchial spread/bronchiolitis), CO-RADS 3 (indeterminate: unifocal GGO), CO-RADS 4 (high level of suspicion: unilateral multifocal GGO) and CO-RADS 5 (very high level of suspicion: multifocal bilateral GGO).
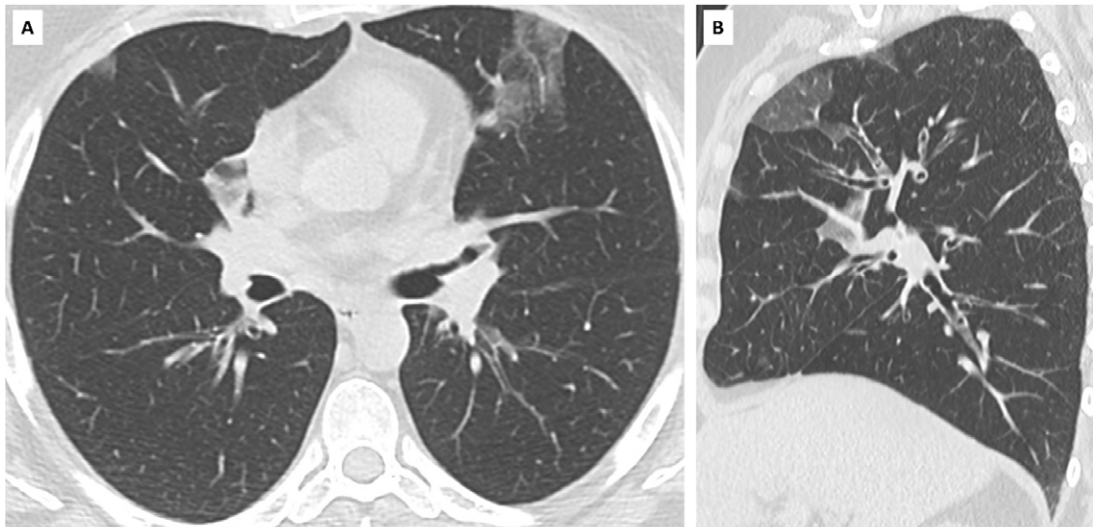
Figure 4: False positive CO-RADS 5 in SARS-CoV-2 PCR-negative symptomatic individual. *A,* axial and, *B,* sagittal CT scan of symptomatic individual with CO-RADS 5 but negative SARS-CoV-2 PCR test. Clinical summary: a 49 year old woman with medical history of haemochromatosis and psoriatic arthritis was admitted with wheezing, dry cough and increasing dyspnea since 2 weeks. She was subfebrile and hypoxic (89% SpO2). Blood testing showed increased CRP (32.8 mg/L) and leukocytosis with eosinophilia (1.1 x 10e3/µl). CT showed no pleural effusion but presence of multifocal bilateral ground glass opacities, scored as CO-RADS 5. SARS-CoV-2 PCR was repeatedly negative on nasopharyngeal swab. Extended syndromic PCR testing for 33 respiratory pathogens including 14 respiratory viruses was negative. Bronchoalveolar lavage was also repeatedly negative for SARS-CoV-2 PCR but showed high load of eosinophils (52 % of 65 x 10e4 nucleated cells/mL) supporting the diagnosis of acute eosinophilic pneumonia. The woman was successfully treated with corticosteroids.
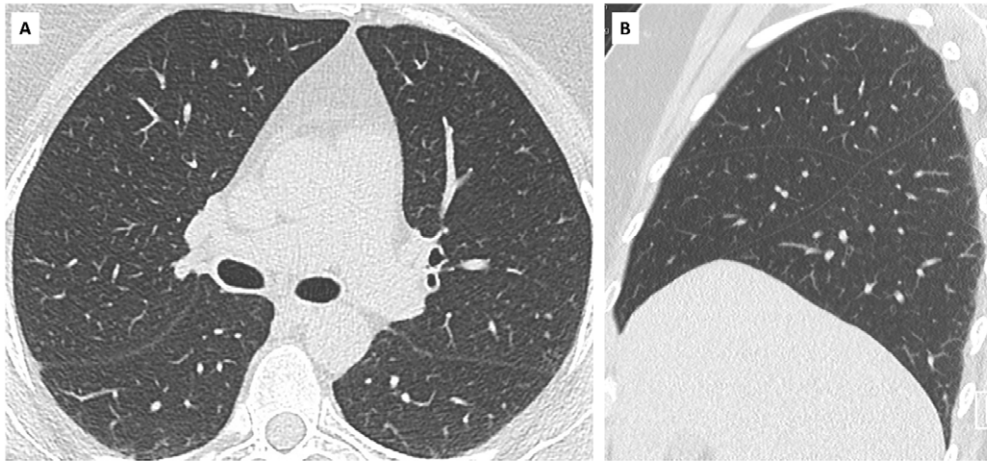
Figure 5: False negative CO-RADS 1 in SARS-CoV-2 PCR-positive symptomatic individual. *A,* axial and, *B,* sagittal CT scan of symptomatic individual with CO-RADS 1 and positive SARS-CoV-2 PCR test. Clinical summary: 57-year old woman presented headache, flu-like symptoms and dry cough for more than 10 days since returning from Hanoi, Vietnam. She was subfebrile and blood testing showed slightly increased CRP (5.3 mg/L), normal leukocyte count, no lymphocytopenia and normal D-dimers and LDH. Chest CT showed no abnormalities. PCR for Influenza A/B and RSV was negative but SARS-CoV-2 PCR was positive.
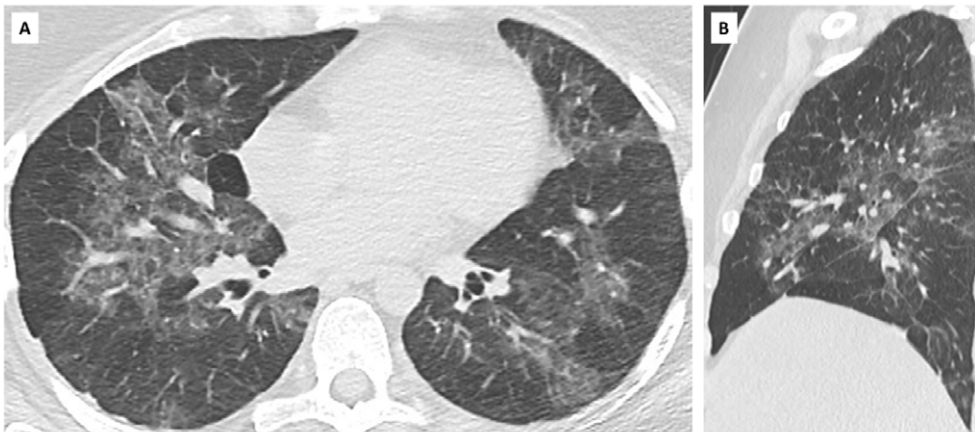

Figure 6: True positive CO-RADS 5 in SARS-CoV-2 PCR-positive asymptomatic individual. *A,* axial and, *B,* sagittal CT scan of asymptomatic individual with CO-RADS 5 and positive SARS-CoV-2 PCR. Clinical summary: a 31 year-old woman was admitted with diarrhea and left iliac fossa pain. She presented no respiratory symptoms, myalgia, loss of taste or smell or abnormal fatigue. Fever (39.4%) was attributed to suspected diverticulitis but a CT abdomen was negative. Standard chest CT scan as part of COVID-19 infection control policy showed multifocal bilateral ground glass opacities and crazy paving pattern, scored as CO-RADS 5. Blood testing showed increased CRP (48.4 mg/L), normal leukocyte count (6.8 x 10e3/μl) and no lymphocytopenia but increased D-dimers (1428 ng/mL) and increased LDH (669 U/L).

Appendix E1
Supplementary Methods: Detailed CT Scanning Protocol

All study participants were imaged by MDCT using either of the following CT scanners: the GE LightSpeed VCT scanner (1-mm slice thickness), Siemens Somatom AS (1-mm slice thickness) or the GE Optmima 660 scanner (1.25-mm slice thickness). Tube voltage = 120 kVp, automatic tube current modulation 30-70 mAS, DLP median 520 (310-906) mGy*cm, estimated mSv median 7,6 mSv (4,2-11,2). All scans were performed without intravenous contrast with the participant in the supine position during end-inspiration. Only the initial CTs were included; follow-up CTs during the study time window were not analyzed.

Image Viewing and Evaluation Two cardiothoracic radiologists with 24 and 9 years of experience retrospectively reviewed all the CT exams on a PACS workstation (IDS7, Sectra) with multiplanar reconstruction tools. Reviewers were blinded to symptomatic versus asymptomatic state and SARS-CoV-2 PCR result. Decision was reached by consensus.

For each study participant, the chest CT scan was evaluated for the following characteristics: (1) presence of ground-glass opacities (early stage, "**stage 1**"), (2) presence of crazy paving pattern (progressive stage, "**stage 2**"), (3) presence of consolidation (peak stage, "**stage 3**"), (4) number of lobes affected where either ground-glass / consolidative opacities were present, (5) degree of involvement of each lung lobe in addition to overall extent of lung involvement measured by means of a "CT-severity score" as detailed below, (6) presence of a pleural effusion, (7) presence of pericardial effusion, (8) presence of thoracic lymphadenopathy (defined as lymph node size of ≥10 mm in short-axis dimension), (10) airways abnormalities (including bronchiectasis, bronchial wall thickening and endoluminal secretions), (11) craniocaudal and anteroposterior distribution of disease (12) presence of underlying lung disease such as emphysema or fibrosis. Each of the five lung lobes was assessed for degree of involvement and classified as none (0%), discrete (<5%), minimal (5 - 25%), mild (26 - 50%), moderate (51 - 75%), or severe (> 75%). No involvement corresponded to a lobe score of 0, discrete to a lobe score of 1, minimal to a lobe score of 2, mild to a lobe score of 3, moderate to a lobe score of 4, and severe to a lobe score of 5. An overall lung "CT-severity score" was reached by summing the five lobe scores (range of possible scores, 0 - 25). CT-severity score was not used in the current study.

The stage was estimated by consensus evaluation of the predominant radiological presentation: ground-glass opacities (early stage, 0-4 days, "stage 1"), (2) presence of crazy paving pattern (progressive stage, 5-8 days, "stage 2"), (3) presence of consolidation (peak stage, 10-13 days, "stage 3") [2]

The Dutch CO-RADS (COVID-19 Reporting and Data System) classification system was used to categorize the level of COVID-19 suspicion, exactly as described [2]. CO-RADS score ranges from 1 (very low level of suspicion), 2 (low level), 3 (equivocal), 4 (high level of suspicion) to 5 (very high level of suspicion).

References

1.   Bernheim A, Mei X, Huang M, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 2020: 200463.

2.   Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS - A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology 2020: 201473.