



# CT and clinical assessment in asymptomatic and pre-symptomatic patients with early SARS-CoV-2 in outbreak settings

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## Abstract

**Objectives** The early infection dynamics of patients with SARS-CoV-2 are not well understood. We aimed to investigate and characterize associations between clinical, laboratory, and imaging features of asymptomatic and pre-symptomatic patients with SARS-CoV-2.

**Methods** Seventy-four patients with RT-PCR-proven SARS-CoV-2 infection were asymptomatic at presentation. All were retrospectively identified from 825 patients with chest CT scans and positive RT-PCR following exposure or travel risks in outbreak settings in Japan and China. CTs were obtained for every patient within a day of admission and were reviewed for infiltrate subtypes and percent with assistance from a deep learning tool. Correlations of clinical, laboratory, and imaging features were analyzed and comparisons were performed using univariate and multivariate logistic regression.

**Results** Forty-eight of 74 (65%) initially asymptomatic patients had CT infiltrates that pre-dated symptom onset by 3.8 days. The most common CT infiltrates were ground glass opacities (45/48; 94%) and consolidation (22/48; 46%). Patient body temperature ( $p < 0.01$ ), CRP ( $p < 0.01$ ), and KL-6 ( $p = 0.02$ ) were associated with the presence of CT infiltrates. Infiltrate volume ( $p = 0.01$ ), percent lung involvement ( $p = 0.01$ ), and consolidation ( $p = 0.043$ ) were associated with subsequent development of symptoms.

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**Conclusions** COVID-19 CT infiltrates pre-dated symptoms in two-thirds of patients. Body temperature elevation and laboratory evaluations may identify asymptomatic patients with SARS-CoV-2 CT infiltrates at presentation, and the characteristics of CT infiltrates could help identify asymptomatic SARS-CoV-2 patients who subsequently develop symptoms. The role of chest CT in COVID-19 may be illuminated by a better understanding of CT infiltrates in patients with early disease or SARS-CoV-2 exposure.

### Key Points

- *Forty-eight of 74 (65%) pre-selected asymptomatic patients with SARS-CoV-2 had abnormal chest CT findings.*
- *CT infiltrates pre-dated symptom onset by 3.8 days (range 1–5).*
- *KL-6, CRP, and elevated body temperature identified patients with CT infiltrates. Higher infiltrate volume, percent lung involvement, and pulmonary consolidation identified patients who developed symptoms.*

**Keywords** SARS-CoV · Asymptomatic infections · Pneumonia · Virus shedding

### Abbreviations

AI	Artificial intelligence
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
KL-6	Krebs von den Lungen 6
LDH	Lactate dehydrogenase
RT-PCR	Reverse-transcriptase polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SE	Standard error
Se	Sensitivity
Sp	Specificity

### Introduction

The high rate of human-to-human transmission of SARS-CoV-2 [1] is related in part to marked pre-symptomatic transmission [2], when infectiousness peaks. Moreover, the vast majority of infections still remain undocumented [3]. Meanwhile, containment and mitigation heavily rely upon strict compliance with isolation, which depends upon a diagnosis or self-identification via symptoms [4–7]. The asymptomatic population remains an underestimated risk during this epidemic [8–10], and currently sparse data are available to understand the transmission dynamics of this population. Furthermore, asymptomatic patients infected with SARS-CoV-2 shed similar viral burdens [8, 11].

Characterization of this asymptomatic population with early chest CT may clarify transmission dynamics. A better understanding of chest CT in an asymptomatic population with infection may inform prognostic modeling or elucidate potential roles for CT in targeted cohorts with exposure or travel history, as an epidemiologic tool to help contain or mitigate outbreaks. Herein, chest CT was analyzed in initially asymptomatic patients who were reverse-transcriptase polymerase chain reaction (RT-PCR) positive for SARS-CoV-2. CT was

also correlated to clinical and laboratory features and subsequent symptoms, to characterize infection patterns of SARS-CoV-2 virus in outbreak settings.

### Materials and methods

#### Patient cohort

Local Research Board approvals were obtained for this retrospective study based on the regulations at the affiliated sites. Clinical, laboratory, and chest CT features were reviewed from a multinational database of 825 patients who all had laboratory-confirmed SARS-CoV-2 and also underwent baseline chest CT upon presentation. A subset of 74 patients was identified with both a history of exposure to COVID-19 and no symptoms at initial presentation. The 825 total patients included 151 patients from Tokyo, Japan (including 103 passengers and crew from the Diamond Princess cruise ship and 48 community-acquired infections), and 674 patients evaluated in Hubei Province, China (all seen between January 21<sup>st</sup> and April 1<sup>st</sup>, 2020). Screening with chest CT was conducted either because of an exposure history of contact with patients with proven or suspected COVID-19 or because of high exposure risk due to travel to high prevalence regions (outbreak zones in Hubei or on cruise ship). Asymptomatic patients had positive RT-PCR for SARS-CoV-2, but no clinical symptoms (defined at the time as dyspnea, cough, and fever). No patients required intensive care unit hospitalization, intubation, or died during follow-up.

#### Clinical and laboratory features

Clinical features and laboratory measurements, including RT-PCR on the day of admission, can be found in Table 1. Patients in the Tokyo cohort also had immunoglobulins (IgG, IgA, IgM) and the pulmonary inflammation marker, Krebs von den Lungen 6 (KL-6).

## CT features

Chest CTs were obtained within one day of admission. CTs were retrospectively reviewed by radiologists blinded to clinical and laboratory information. Three radiologists manually annotated and segmented lung infiltrates ([www.itksnap.org](http://www.itksnap.org)) and 3 other radiologists reviewed CTs independently for the presence of infiltrates, location, types of infiltrate (ground glass, consolidation, intralobular septal lines [“crazy paving”]), atelectasis, reticulation, mosaic attenuation, number of distinct infiltrates, peripheral or central location of the infiltrates, presence of effusion, bronchial wall thickening, tree-in-bud nodules, and preexisting lung disease (including emphysema, bronchiectasis, and fibrosis). After independent characterization of CT images by each radiologist, discrepancies were present in 12 patients which were sorted out by consensus among the 3 radiologists. Volume and average attenuation of the infiltrate, healthy lung, and whole lung were extracted.

## Deep learning–based lung segmentation

All chest CTs underwent automated whole lung segmentation using artificial intelligence (AI) via a custom deep neural network model. The lung segmentation model was trained using a previously described AH-Net architecture [12]. The extent of lung involvement was calculated from infiltrate volume (segmented manually) divided by the overall lung volumes (segmented by model). The quality of the lung segmentation was jointly and non-independently rated on a scale of 1–5 (5 = near perfect to 1 = highly inaccurate) by 3 radiologists who came to consensus.

## Statistical analysis

Clinical, laboratory, and CT imaging characteristics were analyzed using averages and standard deviations (avg  $\pm$  SD) or total numbers and percentages (#; %). All features were examined for collinearity using a Pearson correlation analysis, with  $|r| > 0.5$  considered to be a moderate or better correlation. To compare groups, an unpaired Student *t* test or a Mann-Whitney *U* test was performed for parametric and nonparametric data respectively. Individual feature performance was evaluated by receiver operating characteristic (ROC) curve, area under the curve (AUC) with standard error (SE), sensitivity (Se), and specificity (Sp). The optimal cutoff point was determined by minimizing the distance between ROC plot and point (0.1).

A preliminary and limited assessment on the feasibility of multivariate logistic lasso regression analysis was performed to identify independently significant features. All features were initially considered for inclusion in

the model. Among multiple models, the model with the highest AUC, Se, Sp, and odds ratio (OR) was chosen. The 95% confidence interval (CI) was also reported for logistic regression analyses. Statistical analyses were performed in R (version 3.6.3).

## Results

### Patient cohorts

Seventy-four patients were initially asymptomatic with RT-PCR positive for SARS-CoV-2. This included 41 patients from Tokyo, Japan, and 33 patients from Hubei, China. The combined population showed an average age of  $54 \pm 18$  years old with females being more represented (43/74; 58%). Based on the epidemiologic history and tracing, 44/74 patients (59%) reported contact with a SARS-CoV-2-infected patient. The observation period for the total asymptomatic study population was  $12.1 \pm 3.1$  days.

The RT-PCR positive study population was separated into three groups based on CT findings and symptoms (Fig. 1). A majority of patients (48/74; 65%) presented with infiltrates on chest CT. Twenty-four of 74 patients (32%) had CT infiltrates, but did not develop clinical symptoms. Twenty-four of 74 patients (32%) had CT infiltrates and then developed clinical symptoms 1–5 days ( $3.8 \pm 1.5$  days) after the CT scan. For patients who developed symptoms, the average duration of symptoms was  $9.7 \pm 2.6$  days with an average observation period of  $13.9 \pm 1.8$  days (Fig. 2). Twenty-six of 74 patients (35%) had no CT infiltrates and no clinical symptoms. No patients in this group without CT infiltrates went on to develop symptoms.

### Characterization of CT infiltrates in asymptomatic patients

A total of 48 asymptomatic patients had COVID-19-related CT infiltrates (Table 2). Twenty-eight of 48 patients (58%) presented bilateral involvement. Only left or right lobes were affected for 12/48 (25%) and 8/48 (17%) of patients, respectively. In the majority of cases, infiltrates were diffuse (23/48; 48%) and involved only inferior lobes in 17/48 (35%) and only superior lobes in 7/48 (15%). All but one CT positive patient presented with a peripheral predominance of these infiltrates.

The most frequently represented imaging feature was ground glass opacity (45/48; 94%), followed by consolidation (22/48; 46%) and intralobular septal lines (13/48; 27%). Ten of 48 patients (21%) had preexisting lung diseases. Figure 3 shows two representative cases

**Table 1** Comparison of clinical, CT findings, and laboratory data for asymptomatic patients with and without COVID-19 related CT findings

		Patients with CT infiltrates ( <i>n</i> = 48)		Patients without CT infiltrates ( <i>n</i> = 26)		<i>p</i> value
		Number	%	Number	%	
Clinical features	Gender (F)	31	65	12	46	0.198
	Smoking habits: current/never/ex	15/30/3	31/63/6	6/18/2	23/69/8	0.741
	Significant past medical history	12	25	9	35	0.635
	Contact with SARS-CoV-2 infected patient	35	73	10	38	0.008*
		Avg	SD	Avg	SD	
	Age (years)	54	17	53	21	0.954
	Body height (cm)	162	7	162	8	1.000
	Body weight (kg)	64	11	63	10	0.502
	BMI	24.5	3.5	23.9	3.4	0.476
	Body temperature (°C)	37.0	0.7	36.6	0.3	4.12 × 10 <sup>-4</sup> *
	Respiratory rate (breaths/min)	16	2	16	2	0.722
	Systolic BP (mmHg)	137	24	136	22	0.964
	Diastolic BP (mmHg)	92	15	86	10	0.038*
	Heart rate (beats/min)	77	18	76	14	0.798
	SpO <sub>2</sub> (%)	98	1	97	3.4	0.216
	RT-PCR positive period (days)	10.2	3.7	11.6	5.3	0.616
Laboratory features	BUN (mmol/L)	4.34	1.57	5.19	1.67	0.064
	Creatinine (μmol/L)	71	19	80	22	0.141
	AST (IU/L)	29	20	25	8	0.831
	ALT (IU/L)	28	28	28	23	0.738
	T-Bil (μmol/L)	5.84	6.48	2.28	4.06	0.280
	γGTP (IU/L)	45	49	32	20	0.653
	Amylase (IU/L)	79	28	85	32	0.464
	LDH (mmol/L)	210	65	179	25	0.187
	Albumin (g/L)	41	4	41	10	0.218
	CRP (mg/L)	10.8	15.8	1.7	2.0	0.001*
	UA (μmol/L)	305	78	297	56	0.735
	PCT (ng/mL)	0.18	0.22	0.23	0.16	0.337
	IgG (mg/L)†	1338	327	1400	325	0.586
	IgA (mg/L)†	271	135	300	131	0.517
	IgM (mg/L)†	88	39	84	43	0.419
	KL-6 (U/mL)†	337	173	227	71	0.021*
	RBC (× 10 <sup>12</sup> /L)	5	1	5	1	0.260
	Hemoglobin (g/L)	141	17	140	20	0.610
	WBC (× 10 <sup>9</sup> /L)	5.37	1.76	6.59	1.98	0.018*
	Platelet (× 10 <sup>9</sup> /L)	224	71	240	70	0.385
	Neutrophil (%)	62.9	11.0	64.5	8.9	0.507
	Lymphocyte (%)	28.3	9.3	26.7	8.2	0.458
	Monocyte (%)	7.1	3.0	6.3	2.3	0.340
	Eosinophil (%)	1.4	1.7	1.8	1.7	0.065
	APTT (time)	29	5	30	4	0.215
	APTT (std)	28	0	28	0	0.284
PT (%)	105	16	97	7	0.095	
PT (INR)	0.97	0.08	1.01	0.05	0.020*	

**Abbreviations:** CT, computed tomography; γGTP, gamma-glutamyl transferase; T-Bil, total bilirubin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; SpO<sub>2</sub>, capillary hemoglobin oxygen saturation; BUN, blood urea nitrogen; CRP, C-reactive protein; UA, uric acid; PCT, procalcitonin; Ig, immunoglobulin; HU, Hounsfield units; LDH, lactate dehydrogenase; PT, prothrombin time; PT (INR), prothrombin time calculated as international normalized ratio; RBC, red blood cell count; WBC, white blood cell count; Avg, average; SD, standard deviation

\**p* < 0.05

† Values were available for Tokyo, Japan, cohort only

of an asymptomatic and pre-symptomatic patient with CT infiltrates.

Radiologists' qualitative rating of the adequacy of the deep learning-based lung segmentation resulted in an average of

4.66, and 90.4% of segmentations achieved a score of 4 or 5 (out of 5). None reported major errors.

Based on manual segmentations, the average volume of the lung infiltrates was 111 ± 144 cm<sup>3</sup> per patient. The average

attenuation of the infiltrates was  $-610 \pm 94$  HU, while non-diseased lung had an average attenuation of  $-830 \pm 42$  HU.

**Correlation of clinical and laboratory data to CT infiltrates**

Collinearity between clinical data, laboratory data, and CT infiltrates was assessed for all asymptomatic patients and displayed as a correlation diagram heat map (Fig. 4). Specific to the CT infiltrates, a positive correlation was found between LDH and both infiltrate volume ( $r = 0.68, p = 2.19 \times 10^{-9}$ ) and percentage lung involvement ( $r = 0.67, p = 2.7 \times 10^{-7}$ ). CRP was positively correlated to infiltrate volume ( $r = 0.54, p = 5.83 \times 10^{-6}$ ).

**Comparison of asymptomatic patients with and without CT infiltrates**

Forty-eight asymptomatic patients had COVID-19-related CT infiltrates and 26 had no CT infiltrates (Table 1). When comparing the groups, a higher proportion of patients with infiltrates reported contact with a SARS-CoV-2-infected patient (73% versus 38%,  $p = 0.008$ ) compared to those without CT infiltrates, whose did not report contact, or who may have had only travel exposure to high prevalence locations. Patients with CT infiltrates also had a slightly elevated body temperature

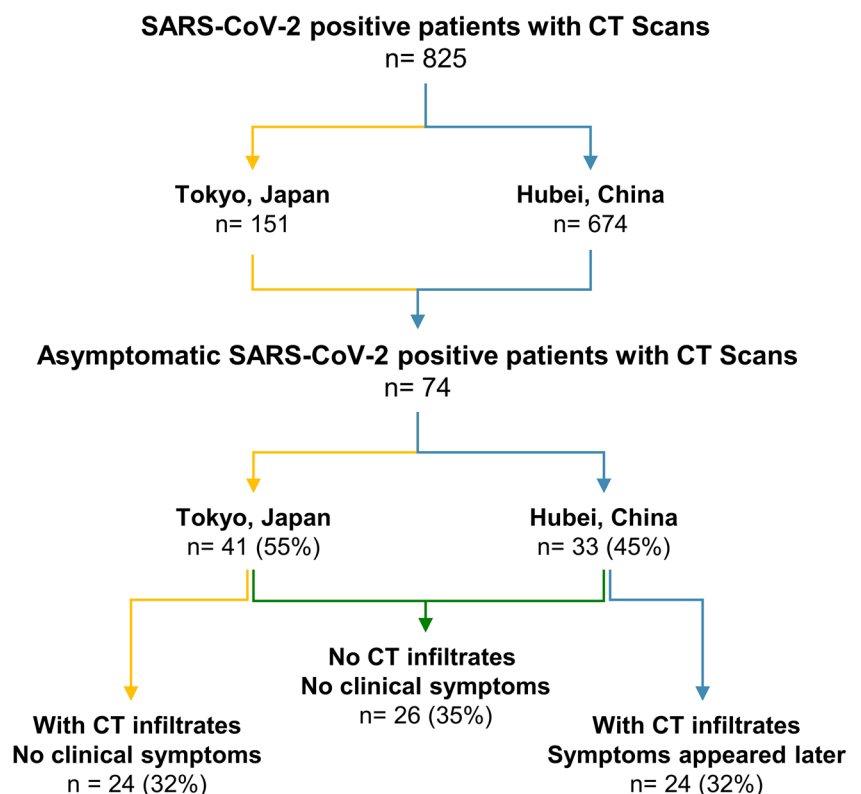
( $37 \pm 0.7$  versus  $36.6 \pm 0.3$  °C,  $p = 4.12 \times 10^{-4}$ ) and diastolic blood pressure ( $92 \pm 15$  versus  $86 \pm 10$  mmHg,  $p = 0.038$ ) compared to those with no CT infiltrates (Table 1).

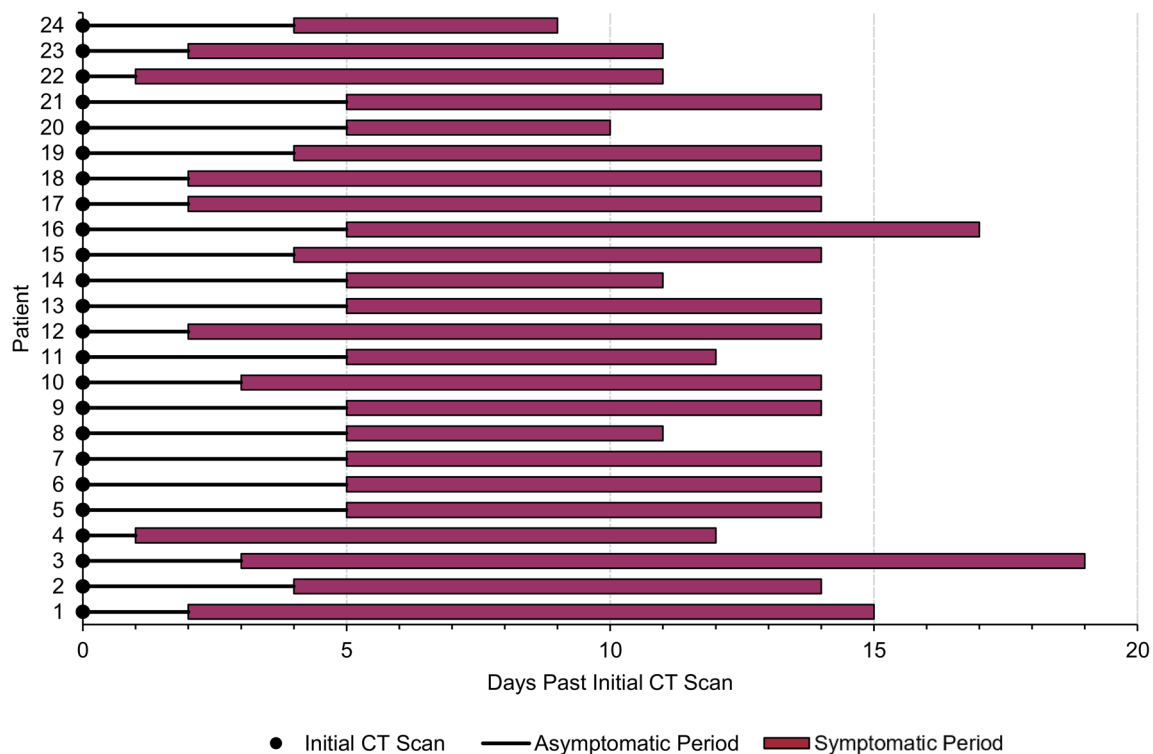
Analysis of laboratory data showed that patients with CT infiltrates had higher CRP ( $10.8 \pm 15.8$  versus  $1.7 \pm 2.0$  mg/L,  $p = 0.001$ ) and KL-6 ( $337 \pm 173$  versus  $227 \pm 71$  U/mL,  $p = 0.021$ ) and lower white blood count ( $5.4 \pm 1.8$  versus  $6.6 \pm 2.0 \times 10^9/L$ ,  $p = 0.018$ ) and PT (INR) ( $0.97 \pm .08$  versus  $1.01 \pm .05$ ,  $p = 0.020$ ) compared to patients with no CT infiltrates.

From the univariate ROC analysis, body temperature (AUC = 0.75, Se = 0.75, Sp = 0.77), CRP (AUC = 0.77, Se = 0.64, Sp = 0.80), and KL-6 (AUC = 0.75, Se = 0.73, Sp = 0.67) were best at distinguishing asymptomatic patients who had CT infiltrates compared to those asymptomatic patients without CT infiltrates (Fig. 5). Table 3 gives ROC analysis and optimal cut points for all parameters found to have  $p < 0.05$ .

From the limited multivariate logistic regression analysis, KL-6 and CRP were independently associated with the presence of COVID-19-related CT infiltrates in asymptomatic patients. The multivariate logistic regression model that included both KL-6 and CRP demonstrated an AUC of 0.84 (SE = 0.068, Se = 0.92, Sp = 0.73, Fig. 5) with an optimal cutoff point of 0.25. Model parameters are given in Table 4.

Fig. 1 Patient selection flow chart





**Fig. 2** Modified swimmer plot of pre-symptomatic patients. Description of patients with CT infiltrates who went on to develop symptoms 1–5 days after initial scan

### Comparison of patients with CT infiltrates who remained asymptomatic versus those who subsequently developed symptoms

Among the 48 asymptomatic patients with CT infiltrates, 24/48 (50%) went on to develop symptoms 1 to 5 days after their initial CT scan ( $3.8 \pm 1.5$  days) (Fig. 2). Twenty-four of 48 patients (50%) never developed symptoms during follow-up (average follow-up 50 days). As expected, the observation period for the asymptomatic patients that never developed symptoms was slightly less than those that developed symptoms ( $11.1 \pm 3.3$  versus  $13.9 \pm 1.8$  days).

A comparison of CT infiltrates found that patients who subsequently developed symptoms had a larger infiltrate volume ( $146 \pm 171$  versus  $76 \pm 103$  cm<sup>3</sup>,  $p = 0.014$ ), higher percent lung involvement ( $3.7 \pm 4.5$  versus  $2.0 \pm 2.7$  %,  $p = 0.013$ ), a lower whole lung attenuation ( $-817 \pm 47$  versus  $-805 \pm 182$  HU,  $p = 0.030$ ), and a higher prevalence of consolidation (63% versus 29%,  $p = 0.043$ ) when compared to patients who did not develop clinical symptoms during follow-up (Table 5).

From univariate ROC analysis, segmentation volume (AUC = 0.71, Se = 0.75, Sp = 0.71) and percent lung involvement (AUC = 0.71, Se = 0.63, Sp = 0.79) were best able to distinguish pre-symptomatic patients from those who remained asymptomatic (Table 3, Fig. 5).

From this limited multivariate analysis, a higher prevalence of consolidation (OR = 4.05, 95%CI = 1.25–14.27) was independently associated with subsequent development of symptoms among the initially asymptomatic patients with CT infiltrates (AUC = 0.67, SE = 0.069, Se = 0.71, Sp = 0.63) with an optimal cut point probability of 0.67; however, the data is limited and likely overfit in the multivariate analysis. The model parameters are given in Table 4.

### Discussion

The role of chest CT in asymptomatic and pre-symptomatic patients with SARS-CoV-2 remains ill-defined. Seventy-four such patients are presented here from 2 different outbreak locations during the COVID-19 pandemic. Dampening the impact of SARS-CoV-2 may depend upon better insight into incompletely understood transmission dynamics. Pre-symptomatic transmission is common [2], and a better understanding could lead to more informed containment and mitigation. CT provides a non-invasive and repeatable informational window into lung infection dynamics in this viral pandemic enigma. Limited reports with small numbers show that CT infiltrates may be present in asymptomatic patients [13–16]. However, pre-test patient selection bias and prevalence likely determine this frequency.

**Table 2** Characterization of the asymptomatic population with CT findings

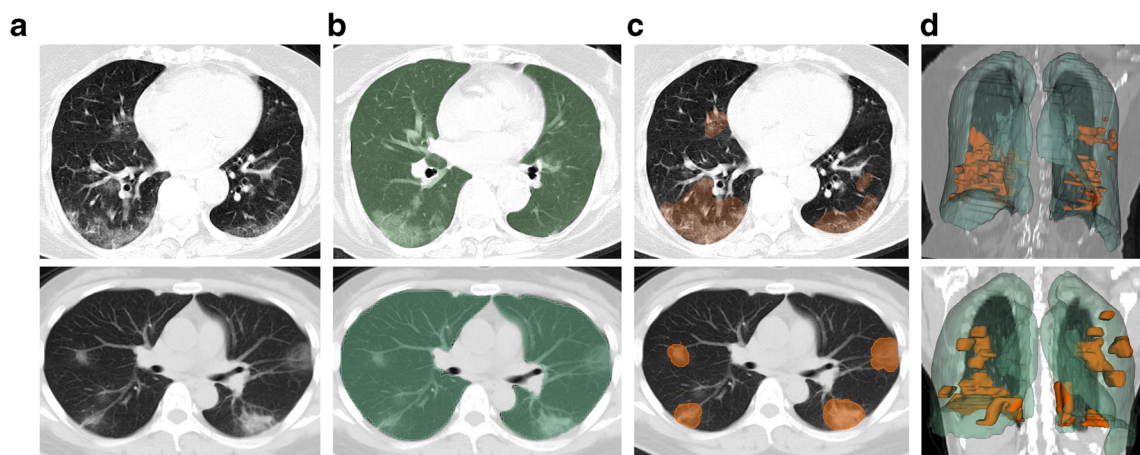
CT finding	Total	% of 48
Patients with CT infiltrates	48	100
Localization		
Bilateral	28	58
Left	12	25
Right	8	17
Diffuse	23	48
Inferior	17	35
Superior	7	15
Peripheral	47	94
Central	0	0
Both peripheral and central	1	2
Infiltrate type		
Ground glass opacity	45	94
Consolidation	22	46
Crazy paving	13	27
Bronchial sign	1	2
Tree in bud	1	2
Pleural effusion	0	0
Preexisting lung disease	10	21
	Avg	SD
Average number of infiltrates	3.9	±3.0
Lung volume		
Infiltrate volume (cm <sup>3</sup> )	111	114
Whole lung volume (cm <sup>3</sup> )	4233	1144
Percent lung involvement (%)	2.9	3.8
Lung attenuation		
Infiltrate attenuation (HU)	- 610	94
Whole lung attenuation (HU)	- 830	42

Abbreviations: CT, computed tomography; HU, Hounsfield unit, Avg, average; SD, standard deviation

Asymptomatic patients with travel or exposure histories may have CT infiltrates, possibly related to SARS-CoV-2 prevalence in high-risk populations. Many passengers with

SARS-CoV-2 from the Diamond Princess Cruise ship were asymptomatic, with 44/82 (54%) of asymptomatic patients having CT abnormalities [17, 18]. However, as with this study, a potential overlap of patients with previously published studies is not possible to evaluate due to requisite de-identification and anonymization processes. This Tokyo cohort differs from previous independent studies in that limited multivariate analysis with continuous lab variables was used here. This study focused on the timing of symptom onset versus CT, and also utilized AI segmentation tools, with additional cohorts from China [19]. During the outbreak in Hubei Province, CT was utilized upfront, alongside RT-PCR, not only at initial symptomatic presentation but also in asymptomatic patients suspected of having COVID-19 after exposure to infected persons or travel to high prevalence or contaminated environments [20]. It is paramount to containment strategies to better understand these asymptotically but infected patients who may silently spread the virus if they remain undiagnosed and un-isolated. Given that CT has detected COVID-19 in some asymptomatic patients before RT-PCR detection of infection [21], a combination of RT-PCR tests and CT may be applied to optimally identify asymptotically but infected patients and their contacts [22].

The proportion of asymptomatic but infected people remains poorly defined [23], but recent estimates showed that up to 80% of COVID-19 patients have mild or asymptomatic [24]. In one study, about 3 in 4 patients with COVID-19 stated they had no known exposure to symptomatic people or potential high-risk environments [1]. Twenty-nine of 33 (88%) of screened SARS-CoV-2-positive pregnant women presenting for delivery in New York City were asymptomatic [25]. These asymptomatic carriers may be responsible for a majority of virus transmission [2, 3, 17].



**Fig. 3** Representative chest CT images of two asymptomatic patients. *Top*—CT scan of a 78-year-old female who never developed COVID-19 symptoms and remained asymptomatic during course of RT-PCR positivity, despite bilateral ground glass opacities on CT. *Bottom*—CT scan of a 41-year-old female who developed symptoms 5 days after CT. Highlighting the higher attenuation of infiltrates, as consolidations. **a**

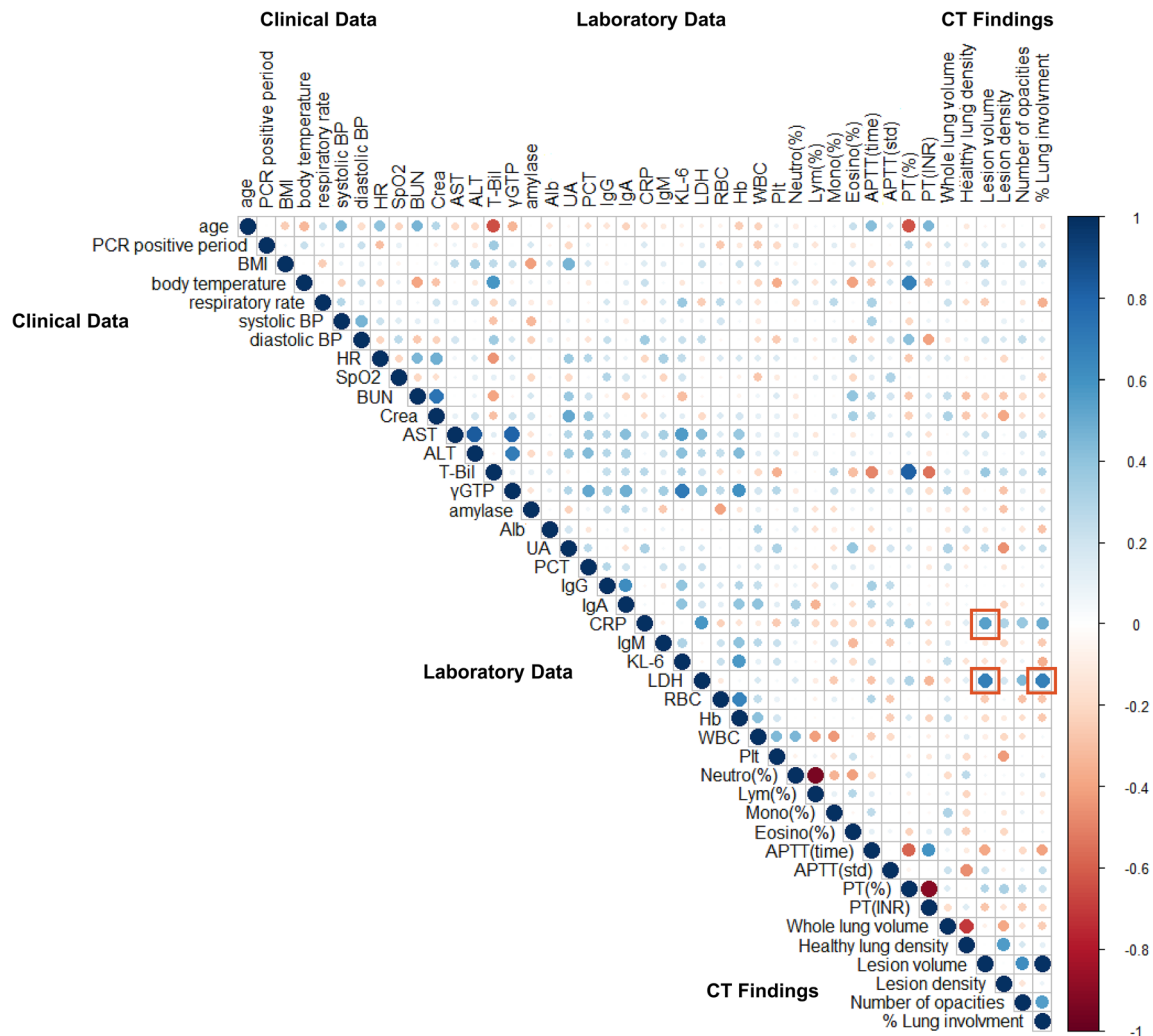
Axial chest CT slice with typical infiltrates of COVID-19 pneumonia. **b** Deep learning-derived whole lung segmentation (green) superimposed over axial chest CT slice. **c** Superimposed segmented infiltrates (orange) over axial chest CT slice. **d** Anterior view of 3D volumes of whole lung (green) and infiltrate (orange) segmentations over a coronal chest CT slice

The transmission dynamics in 94 COVID-19 patients showed the highest viral load, viral shedding, and infectiousness near or before the time of symptom onset, near the end of the incubation period [2]. Although influenza has pre-symptomatic viral replication and infectivity, SARS-CoV-2 infectivity may peak earlier, which complicates detection and isolation strategies [26]. This leaves the exact duration of pre-symptomatic transmission unknown [8]. However, given the mean 5–6-day incubation period for SARS-CoV-2 (range 2–14 days) and that CT was able to detect infection  $3.8 \pm 1.5$  days (1–5 days) before symptoms developed in the present study, the silent progression may be capable of being captured [19].

Additionally, half of 16 patients with COVID-19 presented positive RT-PCR after symptom resolution and may then continue to shed viral RNA [23]. Seroconversion typically occurs after 6 to 12 days,

regardless of RT-PCR status [27], while the median duration of virus shedding by RNA was 20 days in survivors (ranging 8–37 days) [28]. CT is a widely available tool that could be applied in a targeted but limited fashion, to shed light on the critical issue of asymptomatic transmission, or to better define prevalence in specific cohorts. Still, it remains clear that the presence of sub-clinical CT infiltrates in COVID-19 before, after, or irrespective of symptoms remains an enigma.

Several radiology and thoracic professional organizations have recommended against using CT or do not include the role of CT for screening, diagnosis, or contact tracing of COVID-19 [29–31]. Although CT might be useful alongside RT-PCR in the acute setting of early COVID-19 [21], it may suffer from low negative predictive value and specificity, in a low prevalence setting, despite its high sensitivity [32]. Some guidelines



**Fig. 4** Correlation diagram heat map that examines collinearity between clinical, laboratory, and CT findings of asymptomatic patients. Color indicates the value of the correlation coefficient ( $r$ ). The circle size and color intensity are proportional to the correlation coefficient ( $r$ ), with

positive correlations ( $r > 0$ ) shown in red and negative correlations ( $r < 0$ ) shown in blue. A red box highlights a strong positive correlation between LDH and CRP with infiltrate volume and LDH with percent lung involvement



**Table 3** ROC analysis results for independent variables for differentiation of asymptomatic patients with and without CT findings and between patients who developed symptoms later and those who remained asymptomatic.

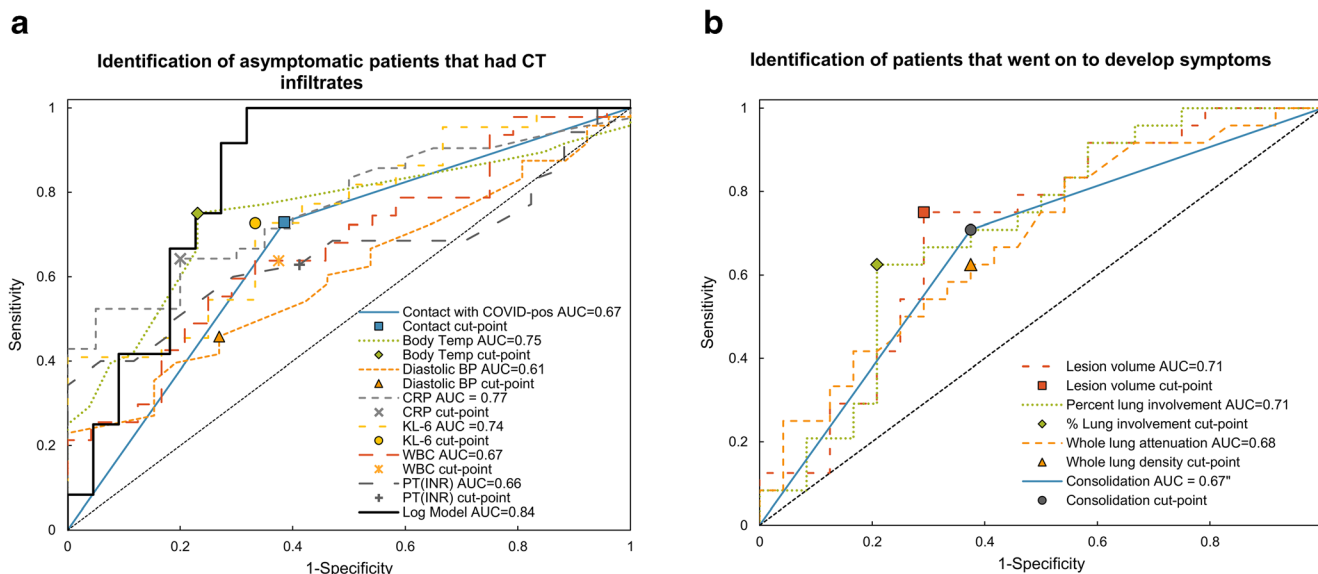
Variable	AUC (upper and lower limit)	SE AUC	Se	Sp	Optimal cut point
Patients with and without CT infiltrates					
Contact with SARS-CoV-2 positive patient (positive)	0.67 (0.56–0.79)	0.058	0.73	0.62	N/A binary
Body temperature	0.75 (0.64–0.86)	0.058	0.75	0.77	36.7 °C
Diastolic blood pressure	0.61 (0.48–0.74)	0.066	0.46	0.73	92 mmHg
CRP	0.77 (0.65–0.88)	0.060	0.64	0.80	2.85 mg/L
KL-6	0.75 (0.58–0.91)	0.085	0.73	0.67	216 U/mL
WBC	0.63 (0.54–0.80)	0.066	0.64	0.67	$5.63 \times 10^9/L$
PT (INR)	0.66 (0.51–0.80)	0.075	0.60	0.71	0.99
Patients who went on to develop symptoms vs. those who remained asymptomatic					
Infiltrate volume	0.71 (0.56–0.86)	0.078	0.75	0.71	59.1 cm <sup>3</sup>
Percent lung involvement	0.71 (0.56–0.86)	0.077	0.63	0.79	1.96%
Whole lung attenuation	0.68 (0.53–0.83)	0.078	0.63	0.63	- 840 HU
Consolidation (present)	0.67 (0.53–0.80)	0.069	0.71	0.63	N/A binary

Abbreviations: AUC, area under curve; SE, standard error; Se, sensitivity; Sp, specificity; CT, computed tomography; CRP, C-reactive protein; PT (INR), prothrombin time calculated as international normalized ratio; WBC, white blood cell count; HU, Hounsfield unit

recommend that CT be reserved for hospitalized symptomatic patients with specific clinical indications [29], which discourages the use of CT in asymptomatic populations to assist with contact tracing. An accurate definition of prevalence including asymptomatic patients could theoretically better inform policy based on epidemiology models to predict early isolation, contact tracing, sentinel surveillance, or back to work strategies. CT

testing carries a low risk of infection for technologists and other healthcare personnel involved in the scans [20]. 3340 CT scans for suspected COVID-19 were performed in one location without a single staff infection reported [33]. Chest CT can also be effective with ultralow radiation doses [34].

CT infiltrates in pre-selected asymptomatic patients with SARS-CoV-2 infection in high prevalence settings



**Fig. 5** ROC analysis of variables to differentiate (a) asymptomatic patients that had CT infiltrates vs. those who did not, and (b) pre-symptomatic patients who went on to develop symptoms vs. those who remained asymptomatic

**Table 4** Model parameters from the limited multivariate logistic regression analysis. The two models predicts the classification in the first group (1)

Multivariate logistic regression model	Estimate	SE	z value	Pr (>)
Model 1: Patients with CT infiltrates (1) vs. patients without CT infiltrate				
Intercept	- 3.606	1.576	2.288	0.022
KL-6	0.0127	0.005	2.317	0.021
CRP	0.269	0.147	1.824	0.068
Model 2: Patients with CT infiltrates who developed symptoms (1) vs. patients without CT infiltrate nor clinical symptom				
Intercept	- 0.636	0.412	- 1.543	0.123
Presence of consolidation	1.398	0.616	2.270	0.023

Abbreviations: SE, standard error; CRP, C-reactive protein; CT, computed tomography

are not uncommon. This occurred in nearly two-thirds of initially asymptomatic patients in this study with exposure history and positive RT-PCR for SARS-CoV-2. CRP and KL-6 levels identified which exposed asymptomatic patients with SARS-CoV-2 had CT infiltrates on presentation. This association is not surprising for markers of inflammation (CRP) and interstitial lung disease or acute respiratory distress syndrome (KL-6). With much more data, it is possible that an elevated yet normal body temperature could also add to predictive models, given the limited association uncovered here in asymptomatic patients with vs without infiltrates. The early identification of patients with specific CT infiltrates, such as consolidation, was able to predict subsequent development of symptoms. This early prognosticator becomes even more important as therapies develop such as Remdesivir, which may be more effective when administered early [35]. Asymptomatic convalescence may also find clandestine CT infiltrates typical for COVID-19 in the presence of negative throat RT-PCR, but positive induced sputum RT-PCR [36].

A major limitation of this study is the small sample size, which limits the ability to implement statistical validation techniques for the multivariate analysis. The multivariate model is likely overfit, which reduces the validity of dependent conclusions. The present findings are merely a demonstration of future work that could include more model data or independent validation and testing. An additional limitation of this study is the retrospective nature, and the selection of RT-PCR positive patients. This limits the ability to further understand the role of CT in the timeframe prior to availability of RT-PCR test results (or with false-negative results in early disease). Our study evaluated patients from 2

**Table 5** Comparison of CT features between asymptomatic patients with CT findings who never developed symptoms and those who went on to develop symptoms 1–5 days after the original CT scan

	Patients with CT infiltrates and no clinical symptoms (n = 24)		Patients with CT infiltrates and symptoms appeared later (n = 24)		p value
	Avg	SD	Avg	SD	
Lung volume					
Whole lung volume (cm <sup>3</sup> )	4231	1067	4235	1239	0.798
Healthy lung volume (cm <sup>3</sup> )	4156	1092	4097	1264	0.976
Infiltrate volume (cm <sup>3</sup> )	76	103	146	171	0.014*
Percent lung involvement (%)	2.0	2.7	3.7	4.5	0.013*
Lung attenuation					
Whole lung attenuation (HU)	- 805	182	- 817	47	0.030*
Healthy lung attenuation (HU)	- 846	30	- 825	47	0.089
Infiltrate attenuation (HU)	- 633	84	- 587	99	0.085
Localization					
	Number	%	Number	%	
Bilateral	12	50	16	67	0.277
Left	6	25	6	25	
Right	6	25	2	8	
Peripheral	24	100	23	96	1.000
Central	0	0	1	4	
Main lobe					
Diffuse	8	33	15	63	0.120
Inferior	11	46	6	25	
Superior	5	21	2	8	
Infiltrate type					
Consolidation	7	29	15	63	0.043*
Ground glass opacity	23	96	22	92	1.000
Crazy paving	10	42	3	13	0.051
Preexisting lung disease	5	21	1	4	0.190
	Avg	SD	Avg	SD	
Number of infiltrates	3.4	2.9	4.4	3.0	0.288

Abbreviations: Avg, average; SD, standard deviation; HU, Hounsfield unit

\*p < 0.05

different sites with heterogeneous clinical protocols, which inevitably presents selection bias and heterogeneity of data, with some missing laboratory data. Furthermore, asymptomatic patients with CT infiltrate came from one cohort, while patients with subsequent symptom onset and CT infiltrates came from another geographic cohort. This cohort difference may introduce other unknown biases related to preselection, CT timing, or other viral exposure differences. However, heterogeneity in general may also enhance generalizability. Independent validation is requisite.

Without defining the exact prevalence within specific outbreak populations, the transmission patterns will remain ill-defined, but 50% of transmissions might be occurring in the pre-symptomatic phase [37]. CT may facilitate characterization in the asymptomatic but exposed populations who are actively shedding. CT scan was able to detect infections at a very early stage of disease, during early incubation, 3.8 days before symptom onset. Although potentially valuable as an addition to RT-PCR in certain settings, the exact role of CT for asymptomatic patients needs to be more clearly defined, especially given its near-immediate availability and turnaround time.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Bradford J. Wood.

**Conflict of interest** NIH and Bradford Wood receive royalties for licensed patents from Philips. NVIDIA and Philips may own intellectual property in the field.

Nicole Varble is an employee of Philips Research.

Dong Yang, Ziyue Xu, Daguang Xu, Mona Flores are employees of NVIDIA corp.

**Statistics and biometry** One of the authors has significant statistical expertise.

**Informed consent** Written informed consent was waived by the Institutional Review Board.

**Ethical approval** Institutional Review Board approval was obtained.

**Study subjects or cohorts overlap** This work is not under consideration elsewhere for publication; however, the Diamond Princess has a broad scope of publications, none of which exactly match these findings or analyses. Please find these selected references:

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## Methodology

- retrospective
- observational
- multicenter study

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