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Diagnostic performance of Chest CT in suspected COVID-19 patients with a negative first RT-PCR testing.
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Abstract:	Background Chest CT could reduce false negative diagnoses of first RT-PCR tests in patients suspected of COVID-19. We aimed to assess the diagnostic performance of CT in patients with a negative first RT-PCR testing and to identify typical features of COVID-19 pneumonia that can guide diagnosis in this case. Methods Patients suspected of COVID-19 with a negative first RT-PCR testing were retrospectively revalued after undergoing CT. CT were reviewed by two radiologists and classified as suspected COVID-19 pneumonia, non COVID-19 pneumonia or negative. The performance of both first RT-PCR result and CT was evaluated by using sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) and by using the second RT-PCR test as the reference standard. CT findings for confirmed COVID-19 positive or negative were compared by using the Pearson chi-squared test (P-values <0.05) Findings 337 patients suspected of COVID-19 underwent CT and nasopharyngeal swabs in March 2020 . 87 out of 337 patients had a negative first RT-PCR result, of these 68 repeated RT- PCR testing and were included in the study.

The first RT-PCR test showed SE 0, SP 100%, PPV = NaN, NPV =70%, AUC = 50%, CT showed SE 70% , SP 79 %, PPV =86%, NPV 76%, AUC=75%.

The most relevant CT variables were ground glass opacity more than 50% and peripheral and/or perihilar distribution.

Interpretation

CT could reduce false negative cases by selecting patients who need a second RT-PCR test.

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TITLE PAGE

Title : Diagnostic performance of Chest CT in suspected COVID-19 patients with a negative first RT-PCR testing.

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INTRODUCTION

On April 25th, Italy reported 195.351 confirmed cases of Coronavirus disease-19 (COVID-19) and 26.384 deaths since the initial outbreak of the disease in Codogno, Italy, in late February.[1]

Clinically, patients suffering from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present fever, cough, dyspnea and muscle aches and bilateral pneumonia on imaging.[2]

Real-time polymerase chain reaction (RT-PCR) on nasopharyngeal swab, is the most frequently used diagnostic method for detecting COVID-19, [3] with a sensitivity ranging from 60 to 71%.[2,4,5] Due to the relatively low sensitivity, swab should be repeated on patients who have symptoms and CT findings suggestive of COVID-19 yet had a negative first test.[5,6]

It has been shown that Computed Tomography (CT) could play a significant role in COVID-19 case screening anticipating RT-PCR positivity.[2,6,7]

Chest CT could reduce false negatives diagnosis of RT-PCR in early stages of disease with a sensitivity of 56-98% in identifying COVID-19 at initial presentation. [4-6, 8–10]

Despite its high sensitivity in diagnosing COVID-19, chest CT had low specificity (25%) as shown in a report of 1014 patients with COVID-19.[2]

Different approaches have been described in managing symptomatic patients following a negative RT-PCR result as rerported in recent guidelines from different countries.[11–17]

According to the recently published Multinational Consensus Statement from the Fleischner Society, in a high pre-test probability environment (according to the cluster or community transmission scenarios defined by the World Health Organization[18]) and in case of resource limitations chest imaging is suggested to provide more rapid identification of patients when RT-PCR COVID-19 testing is not available or initially negative[19].

The aims of this study were to assess the diagnostic perfomance of Chest CT in patients with moderate or high pre-test probability of COVID-19 infection with negative first RT-PCR testing and to identify imaging features typical of COVID-19 pneumonia diagnosis that can be helpful in guiding diagnosis in patients with a negative first RT-PCR.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed, on April, 18th, 2020, for articles describing the diagnostic perfomance of Computed Tomography versus Real Time Polymerase Chain Reaction of upper respiratory tract specimens of suspected patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the search terms (coronavirus OR COVID OR SARS-CoV OR *nCoV*) AND (CT OR

Computed Tomography OR Radio* OR Imag*). We found only very few previously published studies describing the diagnostic performance of CT versus RT-PCR.

We searched PubMed, on April, 18th, 2020, for articles describing the management and guidelines for diagnosis of SARS-CoV-2 infection using the search terms (guidelines OR flowchart OR task force OR statement OR handbook) AND (coronavirus OR COVID OR SARS-CoV2) and we found that for the diagnosis, nucleic acid detection is still regarded as the "gold standard", and that for the majority of guidelines and recommedations nasopharyngeal swab specimen findings are the baseline test for diagnosis in spite of the relatively high false negative results.

Repeated swabs or bronchoalveolar lavage (BAL) are recommended for highly suspected patients. In presence of the above positive findings the patients can be defined as "confirmed cases".

Added value of this study

337 patients suspected of COVID-19 infection with moderate to high pre-test probability according to the transmission scenarios (cluster or community) defined by the World Health Organization, fever and\or respiratory symptoms underwent CT between Mar 1st, 2020 and Mar 29th, 2020 at our department.

On admission, all patients underwent nasopharyngeal swab.

87 out of 337 patients had a negative first RT-PCR result but only 68 out of 87 patients repeated RT- PCR testing to confirm the diagnosis.

We reviewed chest CT images of 68 patients to evaluate the diagnostic performance of CT and to define imaging features that are typical of COVID-19 pneumonia that help to provide early identification of COVID-19 in moderate-highly suspected patients with negative first RT-PCR testing. Our findings provide insight into the primary stratification and identification of suspected Coronavirus disease 2019 (COVID-19) with a false negative result, by combining clinical data with imaging assessment.

Implications of all the available evidence

The role of CT is not clear. The available evidence suggests that due to its high sensititvity in detecting COVID-19 pneumonia, CT could help in the screening of the small proportion of patients who have false-negative RT-PCR results but its positive predictive value could be high only in cluster or community transmission scenarios. Therefore, CT could speed up the diagnosis of COVID-19, improving the control and prevention of the disease when used with caution in according to published guidelines. Further studies are needed to clarify the role of this modality in the control of this infectious disease emergency.

MATERIALS AND METHODS

Patient Population and Study Design

This retrospective study was approved by our local institutional review board (IRB). Informed consent was waived because of the retrospective nature of the study and because the analysis used anonymous clinical data.

Data were extracted from an institutional prospectively maintained database including consecutive patients admitted to the Emergency Department of Humanitas research Hospital in Milan, from March 1st, 2020 to March 29th, 2020.

We included symptomatic patients who underwent CT with moderate or high pre-test probability of COVID-19 infection according to the transmission scenarios (cluster or community) defined by the World Health Organization[19] with moderate or severe respiratory symptoms[11] with a negative first RT-PCR swab with a time-interval between chest CT and the RT-PCR assay of no longer than four days.

Clinical Data

All patients who underwent CT were symptomatic, presenting with fever (temperature >37·5°C), cough and dyspnea.

A patient was considered confirmed as COVID-19 positive or negative after a positive or negative bronchoalveolar lavage or second nasopharyngeal RT-PCR test.

The preferred choice in our hospital was RT-PCR test from bronchoalveolar lavage after a first negative RT-PCR swab.

We excluded patients who did not undergo CT examination or without two RT-PCR tests.

Laboratory data

To confirm the presence of SARS-CoV-2 virus in upper or lower respiratory tract, nasopharyngeal swabs or bronchoalveolar lavage specimens were analyzed with Real Time RT-PCR technique. Two methods were used. One method is based on RNA extraction through high affinity magnetic silica (Biomérieux, France) and amplification with AllplexTM 2019-nCoV Assay (Seegene, Seul, South Korea), a multiplex Real-time PCR assay for simultaneous detection of 3 target genes of SARS-CoV-2 in a single tube with the CFX96TM Real time PCR instrument (Bio-Rad, France). The assay is designed to detect N, E and RdRP genes. The second system detects the same genes,

and was performed on the InGenius instrument (GeneFinder COVID-19 Plus RealAmp kit - ELITech Group, South Korea).

CT Acquisition Technique

As per our hospital COVID-19 protocol, all chest CT acquisitions were obtained with the patients in supine position during end-inspiration without contrast medium injection. Chest CT was performed on a Philips (Netherlands) Brilliance 64 CT scanner dedicated only to patients with suspected COVID-19. The following technical parameters were used: tube voltage: 120 kV; tube current modulation 127 mAs; spiral pitch factor: 1·490; Rotation time 0·4 s, matrix 512. Reconstructions were made at a slice thickness of 2 mm.

The permanence of the patient in diagnostic radiology department was brief (a few minutes or less).

CT Image Analysis

Two radiologists with five and fifteen years of experience (>1000 CT per year) in Chest Imaging, who were blinded to RT-PCR results, reviewed all chest CT images. All patients' identifying information was removed from the CT studies.

Imaging was evaluated by the two radiologists in consensus in terms of the following parameters: [20] (a) multiple lobe involvement, (b) peripheral or perihilar distibution, (c) upper or lower zone distribution, (d) ground-glass opacities (GGO) more than 50% of lung pattern (including crazy paving), (e) consolidation more than 50% of lung pattern, (f) solid nodules, (g) presence of cavitation, (h) ring halo sign, (i) lymphadenopathy (defined as lymph node with short axis > 10mm), (l) pleural and (m) pericardial effusion.

In consideration of the presence of previous findings they assigned the perceived likelihood of COVID-19 infection using this classification: suspected COVID-19 pneumonia, non COVID-19 pneumonia (suggesting other etiology), or negative CT.

If consensus could not be reached, it was resolved by a senior radiologist with more than twenty years of chest CT experience.

Statistical Analysis

Statistical analysis was performed using Matlab version 2019b.

The diagnostic performance of both first RT-PCR result and CT was evaluated by using sensitivity (SE), specificity (SP), diagnostic accuracy, positive predictive value (PPV), negative predictive

value (NPV), and area under the curve (AUC), considering the second RT-PCR test result as the definite result.

CT findings (and variable values) for patients with positive or negative second RT-PCR results were compared by using non-parametric Kruskal-Wallis Test for continuous variables, and with the Pearson chi-squared test, for categorical variables. P-values of $< 0·05$ were considered statistically significant. Such aggregation was computed by iteratively using the Boruta algorithm, [21] and a Random Forest classifier.[22]

The comparison between the medians of the number of days (time) between the onset of symptoms and first naso-oropharyngeal RT-PCR test, Chest CT examination, and second RT-PCR test was expressed through a Win-tie-loss table, where all the win-tie-losses were validated by the Wilcoxon Rank-sign test (95% confidence level).

RESULTS

Patient Population and Clinical Data

337 symptomatic patients with moderate to high pre-test probability of COVID-19 infection underwent CT between Mar 1st, 2020 and Mar 29th, 2020 at our department.

On admission, all patients underwent nasopharyngeal swab.

87 out of 337 patients had a negative first RT-PCR result. 68 out of 87 patients who repeated RT-PCR testing were included in the study.

20 patients out of the 68 had a positive second test result and 48 patients out of 68 had a negative second test result.

19 out of 87 patients who did not repeat RT- PCR test were excluded.

Patient population data is summarized in Table 1.

CT performance

Of 68 CT examinations, 24 were diagnosed suspected of COVID-19 pneumonia (14 patients had a positive second test and ten a negative second test), 31 were diagnosed as Non COVID-19 pneumonia (six patients had a positive second test and 25 a negative second test), and 13 were diagnosed as negative (Table 2).

CT findings in suspected COVID-19 pneumonia and non COVID-19 pneumonia were reported in Table 3 and 4.

The most discriminative features are: ground-glass opacities (GGO) more than 50% of lung pattern (p-value = 0·000040687) multiple lobe involvement (p-value = 0·00025824), peripheral (p-value =

0·00035559), peripheral and perihilar (p-value = 0·0038061) distribution, bilateral distribution (p-value = 0·0046384), pleural effusion (p-value = 0·010927), consolidation more than 50% of lung pattern (p-value = 0·01395), lymphadenopathy (defined as lymph node with short axis > 10mm) (p-value = 0·032051), while the remaining variables do not show any statistical difference between the distribution of COVID-19 positive patients and COVID-19 negative patients. CT findings assessment through statistical testing showed that the most relevant variables are those highlighted by the violet bars in the Figure 1. The classification performance achieved by the most statistically significant variables and the result of aggregating the first three variables (ground-glass opacities more than 50% of lung pattern, peripheral and perihilar distribution, peripheral distribution) are shown in Figure 2. Note that, the addition of more variables (and rules) to the combinations (ground-glass opacities more than 50% of lung pattern and peripheral distribution) and (peripheral and perihilar with peripheral distribution) does not increase performance.

Only ten out of 48 true negative patients were diagnosed as suspected of COVID-19 by CT and six of them had a lung pattern characterized by GGO more than 50%, peripheral with or without perihilar and bilateral distribution. Other lung infections were found only in two out of the six patients (Cytomegalovirus and *Streptococcus pneumoniae*) and the others were diagnosed as Patients with non COVID-19 pneumonia.

The time differences between naso-oropharyngeal RT-PCR and CT scan and second RT-PCR testing were compared, as shown in Figure 3.

The first RT-PCR test showed SE 0 (we analyzed patients with a negative first swab), SP 100%, diagnostic accuracy = 70%, PPV =NaN, NPV =70%, AUC = 50%, CT showed SE 70% , SP 79 %, diagnostic accuracy = 58%, PPV =86%, NPV 76%, AUC=75%. (Table 2).

50 out of 68 patients were confirmed COVID-19 positive (n.15) or negative (n.35) by RT-PCR from bronchoalveolar lavage (BAL), with a duration from onset of symptoms to BAL of $7·5 \pm 0·29$ [min = 1, max = 24] days in positive and $7·5 \pm 0·25$ [min = 2, max = 31] in negative (Table 1 and 5).

12 out of 68 patients were confirmed COVID-19 positive (one) or negative (11) only by the second nasopharyngeal RT-PCR swab with duration from onset of symptoms to second RT-PCR swab of only $5·5 \pm 0·78$ days.

Six out of 68 patients were confirmed COVID-19 positive (four) or negative (two) by the second oro-nasopharyngeal RT-PCR swab and BAL.

The diagnostic performance of CT in combination with a second RT-PCR test achieved a SE of 100%, SP of 79% PPV of 67 %, NPV of 100% and accuracy of 85% (Table 2).

We repeated the statistical analysis of CT performance without the 12 patients who were confirmed COVID-19 positive or negative only by the second naso-oropharyngeal RT-PCR swab and we found SE of 68%, SP of 81%,PPV of 83%, NPV of 76% and accuracy of 74% that confirm better performance of CT than first RT-PCR swab in the identification of false negative cases (Table 2 and 6).

Of the 20 confirmed positive COVID-19 patients, nine patients had other lung co-infection and of the 48 confirmed negative COVID-19 patients 34 had other lung infection (Table 7).

The performance of CT in the differential diagnosis of suspected COVID-19 pneumonia vs non COVID-19 pneumonia and negative CT showed SE of 70%, SP of 79%, PPV of 59 %, NPV of 86% and accuracy of 76% (Table 2).

DISCUSSION

"A role for CT in COVID-19? " was the main question of a recently published letter in The Lancet[23]. We tried to respond to this clinical question and to potentially define the role of CT in patients with a first negative RT-PCR swab.

To date nucleic acid detection with RT-PCR is still the "gold standard" for COVID-19 in spite of its being associated with a false negative rate as high as 50% in a single detection. [14]

Notwithstanding the high specificity, RT-PCR tests can give false negatives results if the sample contains low viral load due to the technique of sample collection or the time when the sample is collected in the course of disease.

WHO guidance[13] advises the collection of lower respiratory tract samples where available from patients who have provided negative upper respiratory samples, but where clinical suspicion of COVID-19 remains, Italian guidelines[12] suggest performing RT-PCR on nasopharyngeal swab every 48-72 hours until persistently negative.

The lack of uniform guidelines in the management of symptomatic patients with negative first RT-PCR result leads to a high level of uncertainty in clinical decisions and the diagnosis.

Recently, the Multinational Consensus Statement from the Fleischner Society has advised chest imaging to support more rapid identification of patients presenting with moderate-to-severe features consistent with COVID-19 infection in a cluster or community transmission scenario, as seen in the North of Italy, when RT-PCR COVID-19 testing is not available or negative. [18]

CT can have a key role in early identification of false negative patients, orienting medical choice and follow up in endemic area.

However, a recent meta-analysis reported that chest CT would not be beneficial in a low-prevalence region.[24]

We evaluated chest CT considering established imaging features that are considered typical of COVID-19 pneumonia[7,8,9,10,20], classifying lung patterns in suspected COVID-19 pneumonia, Non COVID-19 pneumonia and negative CT.[25]

A standardized conclusion of radiological report in terms of suspected COVID-19 pneumonia, Non COVID-19 pneumonia and negative CT could speed up the diagnostic path of patients, suggesting to clinicians to maintain patient in isolation, to repeat RT-PCR test or to make a differential diagnosis with other lung infections or other lung disesases.

It should be borne in mind that COVID-19 pneumonia is difficult to distinguish by imaging from other lung infections caused by influenza A virus, influenza B virus, cytomegalovirus, or other viral pneumonias or bacterial pneumonia or other lung diseases (vasculitis, dermatomyositis and organizing pneumonia).[26,27,28,29]

Our results showed that the most discriminative features of COVID-19 pneumonia were ground-glass opacities (GGO) more than 50% of lung pattern, multilobar involvement with peripheral with or without perihilar distribution and bilateral distribution. The performance of Chest CT in the differential diagnosis of suspected COVID-19 pneumonia vs non COVID-19 pneumonia and negative CT was better aggregating the three most statistically significant variables (GGO more than 50%, peripheral and perihilar or peripheral distribution) with SE of 75%, SP of 83 %, PPV of 65%, and NPV of 89 % and accuracy of 81% (Figure 4).

The presence of these features at first CT examination can be used as imaging biomarker to select patients who need a second RT-PCR test (BAL or repeated nasopharyngeal swab every 48-72 hours until persistently negative).

If BAL or repeated naso-oropharyngeal swab are negative and the radiological pattern is suggestive of COVID-19 in symptomatic patients, is the patient a true negative?

We believe that we have to watch this group of patients who have a suspicious CT, negative second RT-PCR test and without diagnosis of other lung infection or other lung disease. We also feel that further studies are needed to evaluate the role of CT in this condition.

The limitations of our study were the small cohort of patients, the monocentric experience and the unavailability of lung biopsy specimens to evaluate the relationship between radiological and histopathological findings.

In conclusion, CT has "*taught us*"[30] that in presence of the previous CT significative findings the suspicion of COVID-19 should remain high in endemic area, despite a negative first RT-PCR swab and currently second RT-PCR test should be promptly requested to confirm the final diagnosis.

Maybe, in the future serological tests could help to confirm the final diagnosis in patients currently defined as true negative by the second RT-PCR test with suspicious CT and no other lung infection or disease.

Our results should be validated in a larger cohort of patients to confirm the diagnostic perfomance of our imaging criteria in the early identification of false negative patients.

Contributors

C. G. conceived and designed the study.

F. M. S. and G. V. contributed to literature search and to data collection.

E. C. and M. T. S. contributed to acquisition and interpretation of laboratory data.

G.M. F. and A. F. contributed to acquisition and interpretation of clinical data.

E. C. contributed to statistical analysis, to software development, and to data interpretation.

C. G. and E. C. contributed to writing of the report.

L. B., A. C. and A. R. provided critical revision of the article.

All authors approve the final version for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy of the design or integrity of any part of the work have been appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

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FIGURE CAPTIONS

Figure 1. For each timing, the box plots show the median value (circle with spot in the middle), the range from the 25% and the 75% quartiles (heigh of the box), the limits of the spread, and the outliers.

Figure 2. P-values of examined features. Grey bars show not statistically significant features (p-value >=0.05), violet bar highlight statistically significant features (p-value <0.05).

Figure 3. Sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC) for statistically significant features. Colored bars allow a visual comparison of the achieved performance (red for performance measures mainly focusing on positive patients, blue for performance measures mainly focusing on negative patients, yellow for performance measures balancing the performance on positive and negative patients).

Figure 4. A 67-year-old man with a negative first RT-PCR result: ground-glass opacities more than 50% of the lung pattern with peripheral and bilateral distribution in axial and coronal CT planes (A, B). Images were analyzed with the COPD advanced visualization application in ISP (Philips Medical Systems, Best, The Netherlands). The extent of normal aerated lung was in all batches quantified by the percent of lung voxels with attenuation < -660 Hounsfield units (C).
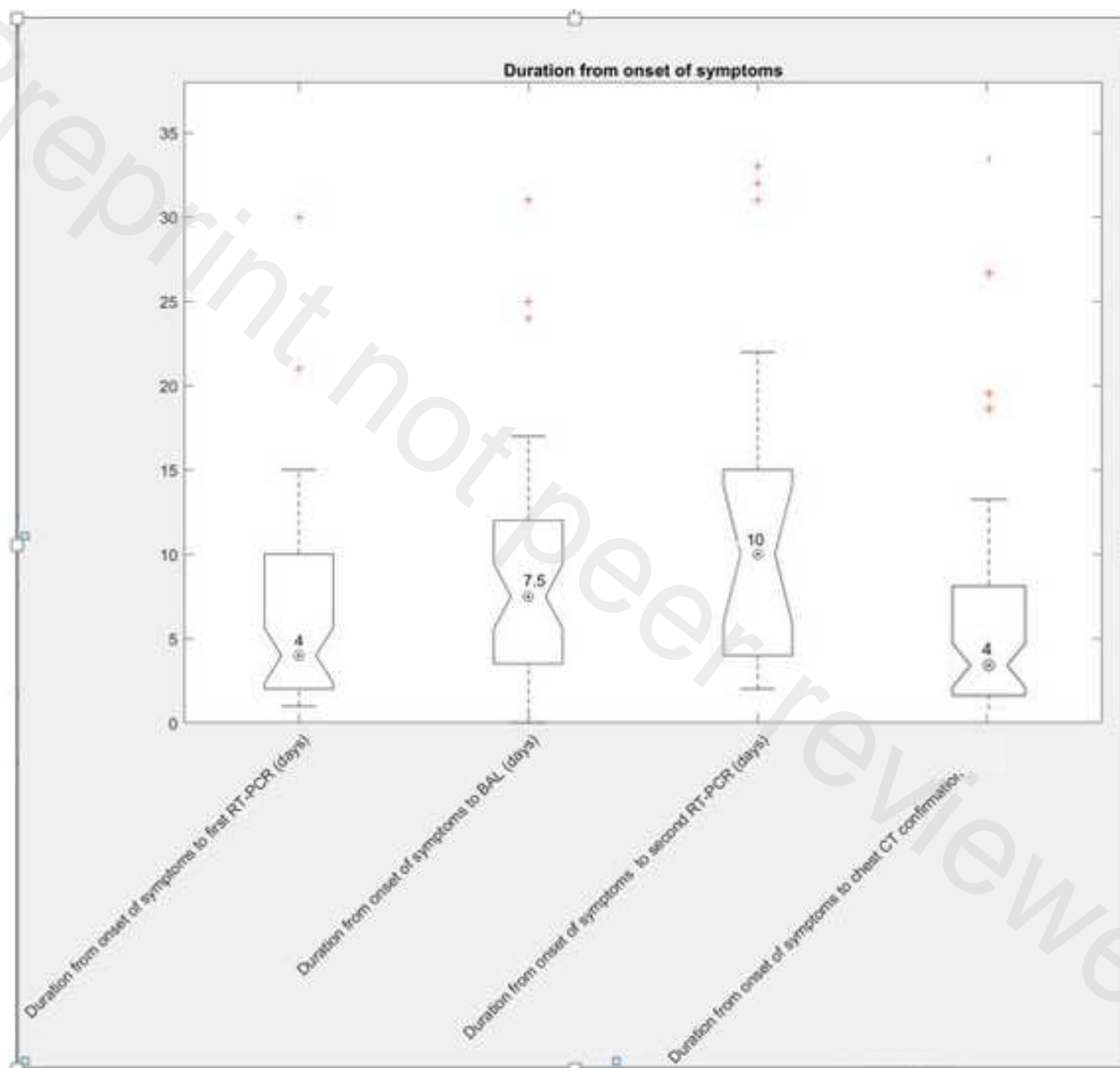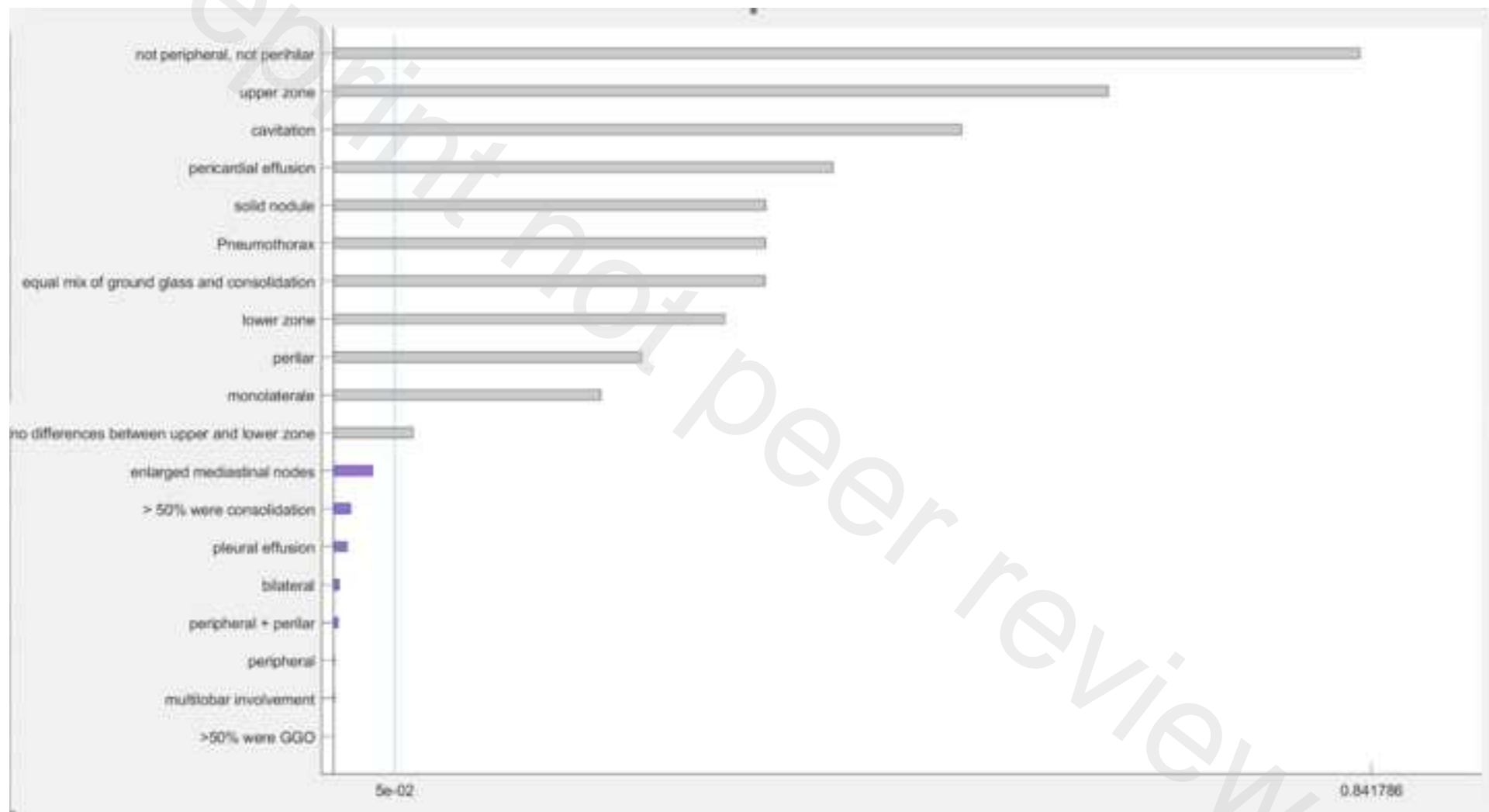
Figure 1   Click here to download Figure Figure 1.JPG ⬇

Duration from onset of symptoms

Figure 2　Click here to download Figure Figure2.png ⬇

Figure 2

Figure 3   Click here to download Figure Figure3.png ⬇

Variable	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC
>50% were GGO	90%	65%	72%	51%	94%	77%
peripheral + perilar	90%	49%	64%	50%	89%	69%
peripheral	85%	63%	69%	49%	91%	74%
multilobar involvement	60%	79%	74%	55%	83%	70%
bilateral	85%	52%	62%	43%	89%	69%
pleural effusion	85%	48%	59%	40%	88%	66%
> 50% were consolidation	95%	33%	51%	37%	94%	64%
enlarged mediastinal nodes	80%	48%	57%	39%	85%	64%
>50% were GGO & peripheral	75%	83%	81%	65%	89%	79%
peripheral & perilar+peripheral	75%	83%	81%	65%	89%	79%

Threshold: - 660 HU

Lungs

	Lung volume = - 660 HU (cm3)	Total lung volume (cm3)	Ratio lung volume (%) Threshold=660 HU
Lungs	2842.6	3592.5	79.1
Right lung	1419.8	1845.1	76.9
Upper right lobe	808.4	955.8	84.6
Middle lobe	353.3	370.6	95.3
Lower right lobe	258.1	518.7	49.8
Left lung	1422.8	1747.3	81.4
Upper left lobe	919.9	1077.7	85.4
Lower left lobe	503	669.6	75.1
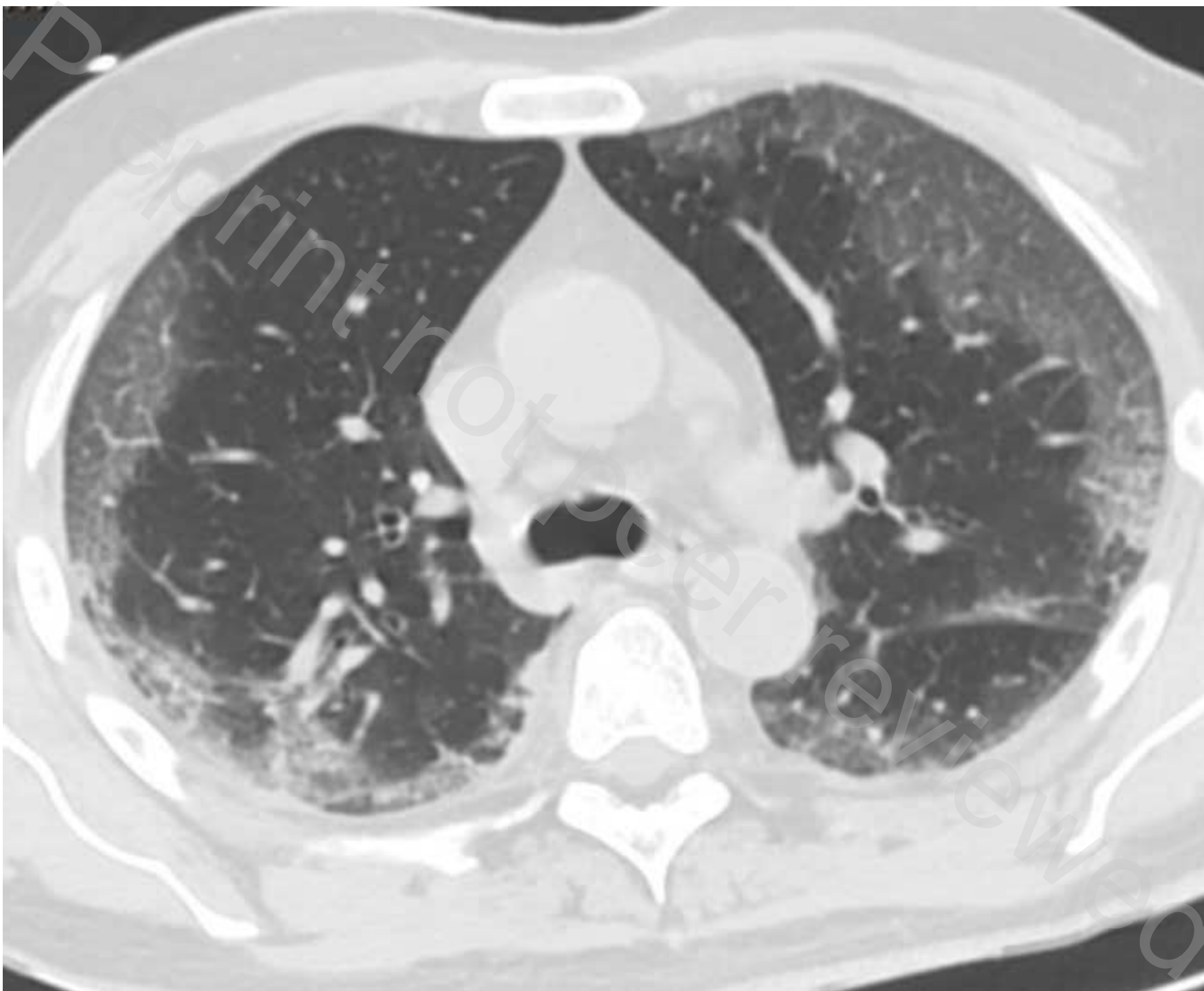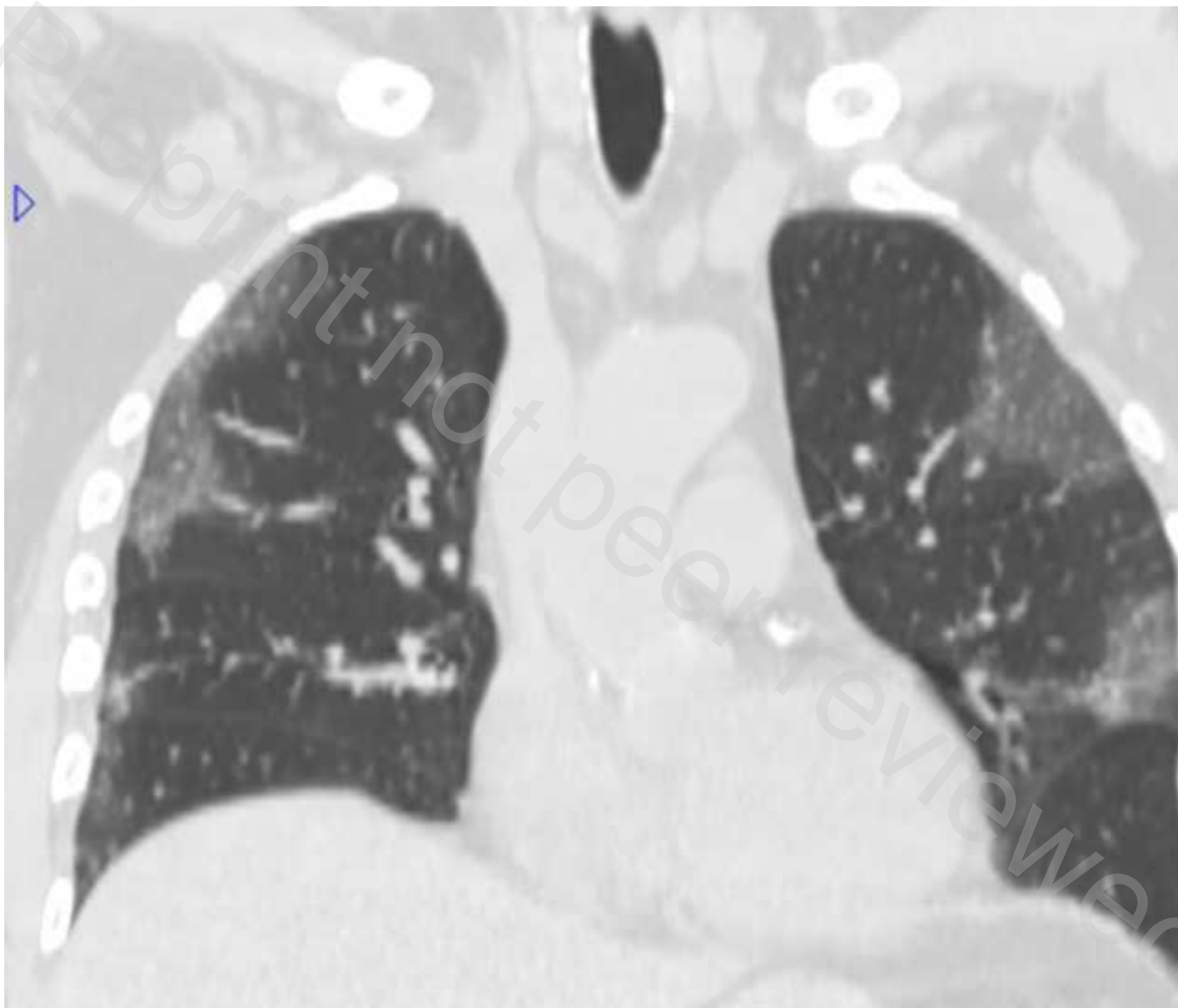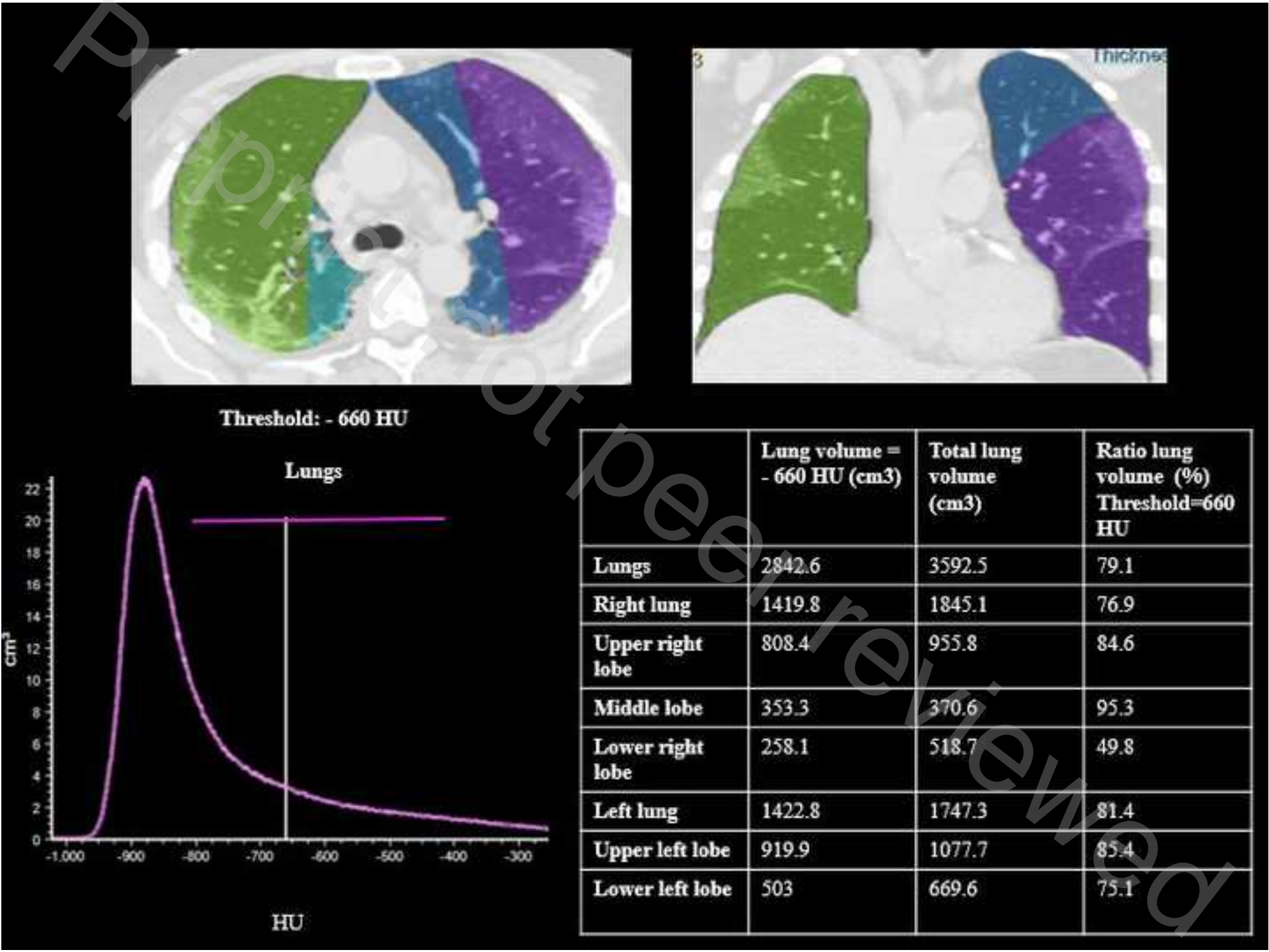
Tables

Table 1. Patient population and clinical-laboratory data.

Patient cardinality for both confirmed Covi19 positive patients, confirmed Covid19 negative patients, and total. To describe the age distribution, median ± standard error [min value, max value] are reported.

	Confirmed COVID19 positive	Confirmed COVID19 negative	Total
Male	18	23	41
Female	2	25	7
Median age	60 ± 3.08 [min = 35, max = 83]	63·5 ±2.19 [min = 26, max = 87]	62.5 ± 1.80 [min = 26, max = 87]
Repeated nasopharyngeal RT-PCR	1	11	12
Bronchoalveolar lavage RT-PCR	15	35	50
Repeated nasopharyngeal RT-PCR and Bronchoalveolar RT-PCR	4	2	6

Table 2. Showed chest CT performance and first RT-PCR performance

Showed chest CT performance in "suspected COVID19 pneumonia" and in "NO Covid19 Pneumonia and negative CT", "first RT-PCR" performance and CT performance in "suspected COVID19 pneumonia with second RT-PCR test"

	Suspected COVID19 vs (No covid19 pneumonia and negative)	NO Covid 19 pneumonia CT findings vs (Suspected Covid19 and negative)	Negative vs (Suspected Covid19 and NO Covid 19 pneumonia CT findings)	First RT-PCR test	Suspected Covid 19 and second RT-PCR test
Duration from ONSET of symptoms median ± s.e. [min value, max value]	7 ± 0.20 [min = 1, max = 22]	4 ± 0.22 [min = 1, max = 30]	2 ± 0.24 [min = 1, max = 10]	4 ± 0.11, [min = 1, max = 31]	**5± 0.59 [min = 0, max = 31]
Confirmed COVID 19 Positive	14	6	0	0	20
Confirmed COVID 19 Negative	10	25	13	68	48
Total	24	31	13	68	68
SE	70%	70%	*100%	0	100%
SP	79%	52%	*27%	100%	79%
PPV	58%	38%	*36%	NaN	67%
NPV	86%	81%	*100%	70%	100%
ACCURACY	76%	57%	*49%	70%	85%
AUC	75%	39%	*36%	50%	89%

*When Negative ct finding is used 100% sensitivity is obtained by considering as positive those patients for which the ct is NOT negative.

**The median duration is computed with respect to the second RT-PCR test.

Table 3. CT findings for suspected COVID19 Pneumonia.

For each CT finding related to suspected COVID19 Pneumonia we report the proportion of Covid19 positive patients and Covid19 negative patients at second test.

	Covid19 positive at second test	Covid19 negative at second test
Multiple lobe involvement	13\14	10\10
Bilateral	13\14	9\10
Peripheral distribution	11\14	3\10
Perihilar distribution	0\14	0\9
Peripheral and perihilar distribution	2\14	7\10
Not peripheral and not perihilar distribution	1\14	0\10
Upper zone distribution	7\14	3\10
Lower zone distribution	1\14	4\10
No difference between upper and lower zone	6\14	3\10
Ground glass opacities more than 50% of lung pattern	13\14	6\10
Consolidation more than 50% of lung pattern	0\14	4\10
Equal mixed ground glass opacities and consolidation	1\14	0\10
Solid nodules	0\14	0\10
Cavitation	0\14	1\10
Ring halo sign	0\14	0\10
Lymphadenopathy	0\14	5\10
Pleural effusion	2\14	6\10
Pericardial effusion	2\14	1\10

Table 4. CT findings for No COVID19 Pneumonia

For each CT finding related to No COVID19 Pneumonia we report the proportion of Covid19 positive patients and Covid19 negative patients at second test.

	Covid19 positive at second test	Covid19 negative at second test
Multiple lobe involvement	6\6	14\25
Bilateral	4\6	12\25
Peripheral distribution	6\6	11\25
Perihilar distribution	0\6	1\25
Peripheral and perihilar distribution	0\6	10\25
Not peripheral and not perihilar distribution	0\6	3\25
Upper zone distribution	0\6	9\25
Lower zone distribution	4\6	10\25
No difference between upper and lower zone	2\6	6\25
Ground Glass opacities more than 50% of lung pattern	5\6	11\25
Consolidation more than 50% of lung pattern	1\6	12\25
Equal mixed Ground glass opacities and consolidation	0\6	2\25
Solid nodules	0\6	1\25
Cavitation	0\6	0\25
Ring halo sign	0\6	0\25
Lymphadenopathy	1\6	15\25
Pleural effusion	1\6	11\25
Pericardial effusion	0\6	2\25

Table 5. Duration from onset of symptoms

Duration form onset of symptoms to first RT-PCR, to BAL, and to second RT-PCR. Durations are expressed in days. For each duration, median ± standard error [min value, max value] are reported.

	Confirmed Covid 19 Positive	Confirmed Covid 19 Negative
Duration from onset of symptoms to first RT-PCR (days)	7 ± 0.24 [min = 1, max = 21]	3.5 ± 0.16 [min = 1, max = 30]
Duration from onset of symptoms to BAL (days)	7.5 ± 0.29 [min = 1, max = 24]	7.5 ± 0.25 [min = 2, max = 31]
Duration from onset of symptoms to second RT-PCR (days)	13.5 ± 1.86 [min = 7, max = 33]	5.5 ± 0.78 [min = 2, max = 32]

Table 6. Chest CT performance in suspected COVID-19 pneumonia and in non COVID-19 pneumonia and negative CT, in patients confirmed COVID-19 positive or negative by bronchoalveolar lavage RT-PCR test.

	Suspected COVID-19 vs (non COVID-19 pneumonia and negative)	non COVID-19 pneumonia CT findings vs (Suspected COVID-19 and negative)	Negative vs (suspected COVID-19 and non COVID-19 pneumonia CT findings)
Duration from ONSET of symptoms median ± s.e. [min value, max value]	7 ± 0.24 [min = 1, max = 22]	4 ± 0.24 [min = 1, max = 30]	3 ± 0.53 [min = 1, max =7]
Confirmed COVID-19 Positive	13	6	0
Confirmed COVID-19 Negative	7	24	5
Total	20	30	5
SE	68%	32%	*100%
SP	81%	33%	*14%
PPV	65%	20%	*38%
NPV	83%	48%	*100%
ACCURACY	76%	33%	*44%
AUC	74%	32%	*57%

Table 7. Other confirmed infections in COVID-19 positive patients and COVID-19 negative patients at second test.

For each of the observed infection we report the observed number\total number of COVID-19 positive (20) or COVID-19 negative (48) patients at second test.

Other infections	Covid19 positive at second test	Covid19 negative at second test
Streptococcus pneumoniae	5\20	4\48
,Pneumocystis jiroveci	1\20	0\48
Candida Albicans	1\20	1\48
Aspergillus	1\20	0\48
Escherichia coli	1\20	0\48
Klebsiella pneumoniae	0\20	1\48
Cytomegalovirus	0\20	1\48
Pseudomonas	0\20	1\48
Staphylococcus aureus	0\20	2\48
Streptococcus pneumonia with Enterococcus	0\20	1\48
Escherichia coli and aerobic species	0\20	1\48
Streptococcus pneumonia with Enterococcus and Candida albicans	0\20	1\48
Klebsiella pneumoniae and Enterococcus	0\20	1\48
Para-influenzal virus with Epstein Barr Virus and Cytomegalovirus	0\20	1\48
,Pneumocystis jiroveci and Moraxella	0\20	1\48
Staphylococcus aureus, Cytomegalovirus, Pneumocystis jiroveci	0\20	1\48
Pneumocystis jiroveci, Metapneumovirus	0\20	1\48
Staphylococcus aureus,Klebsiella pneumoniae, Rhinovirus	0\20	1\48
Staphylococcus aureus, Legionella, Cytomegalovirus	0\20	1\48
Strenotrophomonas	0\20	2\48
Unknown etiology	0\20	12\48