CHEST RADIOLOGY

Chest CT in patients with a moderate or high pretest probability of COVID-19 and negative swab

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Abstract

Objectives 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 was 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)

Results Totally, 337 patients suspected of COVID-19 underwent CT and nasopharyngeal swabs in March 2020. Eighty-seven 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%, and 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.

Discussion Negative RT-PCR test but positive CT features should be highly suggestive of COVID-19 in a cluster or community transmission scenarios, and the second RT-PCR test should be promptly requested to confirm the final diagnosis.

Keywords COVID-19 · RT-PCR · Nasopharyngeal swab · Computed tomography

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Introduction

On May 24, Italy reported 229,858 confirmed cases of coronavirus disease-19 (COVID-19) and 32,785 deaths since the initial outbreak of the disease in Codogno, Italy, in late February [1].

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

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

CT could play a significant role in COVID-19 case screening anticipating RT-PCR positivity [2, 6, 7].

Chest CT could reduce false-negative diagnosis of RT-PCR in the early stages of the 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 are possible in managing symptomatic patients following a negative RT-PCR result, as reported in recent guidelines from different countries [11–17].

According to the Multinational Consensus Statement from the Fleischner Society, in a high pretest 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 rapid identification of patients with COVID-19 is imperative during an outbreak of a highly infectious disease. An initial false-negative result could delay treatment and increase the risk of viral transmission to others.

This study aimed to describe the diagnostic performance of chest CT in patients with a moderate or high pretest probability of COVID-19 infection, with negative RT-PCR testing. We also aimed at identifying imaging features typical of COVID-19 pneumonia diagnosis, which can help suggest a diagnosis in patients with a negative RT-PCR.

Materials and methods

Patient population and study design

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

Data were extracted from an institutional prospectively maintained database, including consecutive patients admitted to our Emergency Department, from March 1, 2020, to March 29, 2020.

We included symptomatic patients who underwent CT with a moderate or high pretest 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] and a negative RT-PCR swab. The time-interval between chest CT and the RT-PCR assay was 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 as COVID-19 positive or negative after a positive or negative bronchoalveolar lavage or a second nasopharyngeal RT-PCR test.

The preferred choice in our hospital was the 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

Nasopharyngeal swabs or bronchoalveolar lavage specimens were analyzed with RT-PCR technique to confirm the presence of the SARS-CoV-2 virus in the upper or lower respiratory tract. 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, Seoul, 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 detected 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 the 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 had a slice thickness of 2 mm.

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.

The two radiologists evaluated imaging in consensus in terms of the following parameters [20]: (a) multiple lobe involvement, (b) peripheral or perihilar distribution, (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 > 10 mm), (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 was not reached, a senior radiologist with more than twenty years of chest CT experience made the final decision.

Statistical analysis

Statistical analysis was performed using MATLAB version 2019b (The Mathworks Inc, USA).

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 nonparametric 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

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

Twenty patients out of 68 had a positive second test result, and 48 patients out of 68 had a negative second test result.

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

Patient population data are summarized in Table 1.

Table 1 Patient population and clinical laboratory data

	Confirmed COVID-19 positive	Confirmed COVID-19 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

Patient cardinality for both confirmed COVID-19-positive patients confirmed COVID-19-negative patients, and total. Age distribution and median ± standard error [min value, max value] are reported

CT performance

Of 68 CT examinations, 24 were diagnosed suspected of COVID-19 pneumonia (14 patients had a positive second test and 10 a negative second test), 31 were diagnosed as non-COVID-19 pneumonia (6 patients had a positive second test and 25 a negative second test), and 13 were diagnosed as negative in consideration of the perceived likelihood of COVID-19 (Table 2).

CT findings in suspected COVID-19 pneumonia and non-COVID-19 pneumonia are reported in Tables 3 and 4.

The most discriminative features were: ground glass opacities (GGO) more than 50% of lung pattern (p value $= 0·000,040,687$), multiple lobe involvement (p value $= 0·00,025,824$), peripheral (p value $= 0·00,035,559$), peripheral and perihilar (p value $= 0·0,038,061$) distribution, bilateral distribution (p value $= 0·0,046,384$), pleural effusion (p value $= 0·010,927$), consolidation more than 50% of lung pattern (p value $= 0·01,395$), lymphadenopathy (defined as lymph node with short axis > 10 mm) (p value $= 0·032,051$), while the remaining variables did 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 Fig. 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 Fig. 2 and 3. 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. The time differences between naso-oropharyngeal RT-PCR and CT scan and second RT-PCR testing (BAL or second nasopharyngeal swab) were compared, as shown in Fig. 4.

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).

Twenty out of 68 patients were false-negative cases of the first RT-PCR test, 10 out of 68 patients were false-positive cases of CT, and six out of 68 patients were false-negative cases of CT.

Fifty 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.

Twelve out of 68 patients were confirmed COVID-19 positive (1) or negative (11) only by the second nasopharyngeal

Table 2 Chest CT performance, first RT-PCR performance, chest CT and second 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)	First RT-PCR test	Chest CT in suspected COVID-19 pneumonia and second RT-PCR test
Duration from onset of symptoms median $\pm$ 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	20	20
Confirmed COVID-19 negative	10	25	13	48	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%

Chest CT performance in "suspected COVID19 pneumonia" and in "Non-Covid19 Pneumonia" and "negative CT," "first RT-PCR" performance, and CT performance in "suspected COVID19 pneumonia with second RT-PCR test"

*When Negative CT finding is used, 100% sensitivity is obtained by considering as positive those patients for whom the CT is not negative

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

Table 3 CT findings for suspected COVID-19 pneumonia

	Confirmed COVID-19 positive at second test	Confirmed COVID-19 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

For each CT finding related to suspected COVID-19 pneumonia, we report the proportion of COVID-19-positive patients and COVID-19-negative patients at the second test

Table 4 CT findings for no COVID-19 pneumonia

	COVID-19 positive at second test	COVID-19 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

For each CT finding related to non-COVID-19 pneumonia, we report the proportion of COVID-19-positive patients and COVID-19-negative patients at the second test

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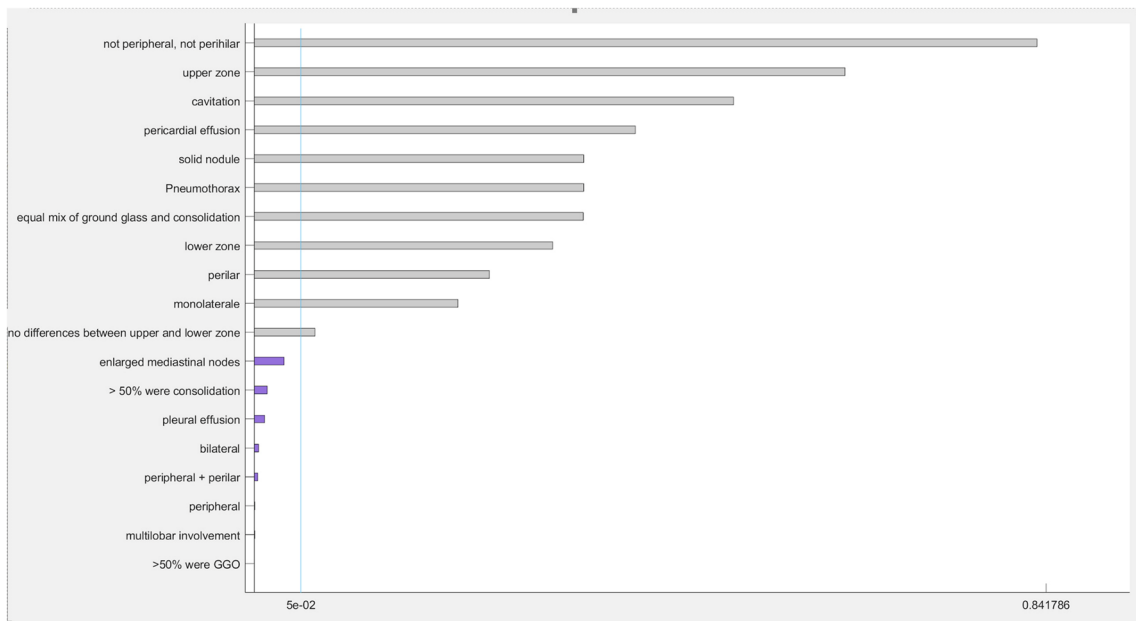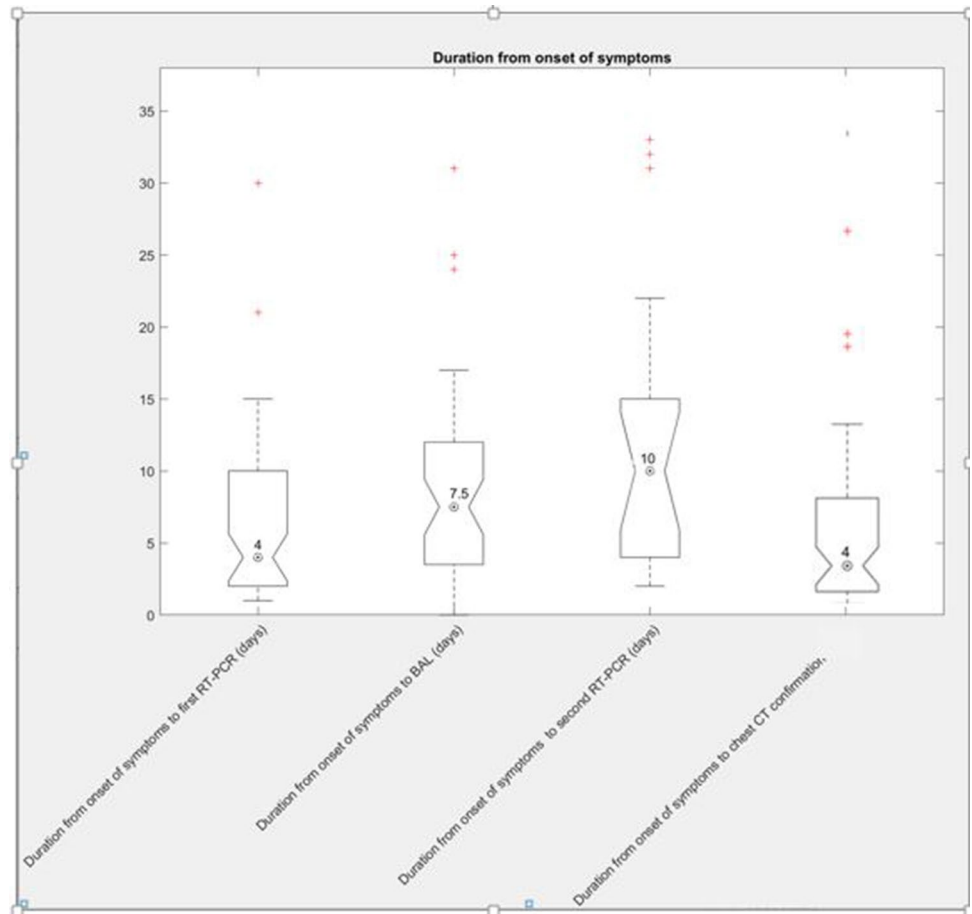

Fig. 2 *P* values of examined features. Grey bars show not statistically significant features (p value $>= 0.05$), violet bars highlight statistically significant features (p value < 0.05)

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%

Fig. 3 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 the aerated lung was in all batches quantified by the percent of lung voxels with attenuation < -660 Hounsfield units (C)

RT-PCR swab with the 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 the better performance of CT than first RT-PCR swab in the identification of false-negative cases.

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 another lung infection (Table 5).

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

To date, nucleic acid detection with RT-PCR is the "gold standard" for COVID-19 diagnosis despite 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-negative 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 the disease.

The use of CT for COVID-19 diagnosis is controversial. It can have a crucial role in the early identification of false-negative patients, orienting medical choice and follow-up in the endemic area.

A meta-analysis of Kim et al. [23] showed that the pooled sensitivity was 94% for CT and 89% for RT-PCR, and the pooled specificity of chest CT was 37%. The authors evaluated the estimated predictive values of CT and RT-PCR for COVID-19 in Italy. The PPV was 24.5% for CT and 95.1% for RT-PCR; the NPV was 96.6% for CT and 97.6% for RT-PCR.

In the studies [2, 24–28] included in the meta-analysis of Kim et al. [23], the diagnostic performance of CT versus RT-PCR was evaluated in patients with positive and negative first RT-PCR, considering CT as a screening tool.

We aimed to focus on patients with a first negative RT-PCR test to evaluate the added value of CT in this condition.

Our results confirmed a higher sensitivity and lower specificity of CT (SE 70%, SP 79%) in respect of a negative RT-PCR test (SE 0%, SP 100%).

The limitations of RT-PCR are false-negative cases, while of CT are false-positive ones. In our experience, the number of false-positive CT cases was lower than the RT-PCR false-negative cases.

The low specificity of CT is due to the overlap of CT imaging features between COVID-19 and other viral pneumonia and lung conditions. In fact, in 3 out of 6 false-negative CT cases, another lung infection was diagnosed.

It should be noted that COVID-19 pneumonia is difficult to distinguish by imaging from influenza A virus, influenza B virus, cytomegalovirus, or other viral pneumonia
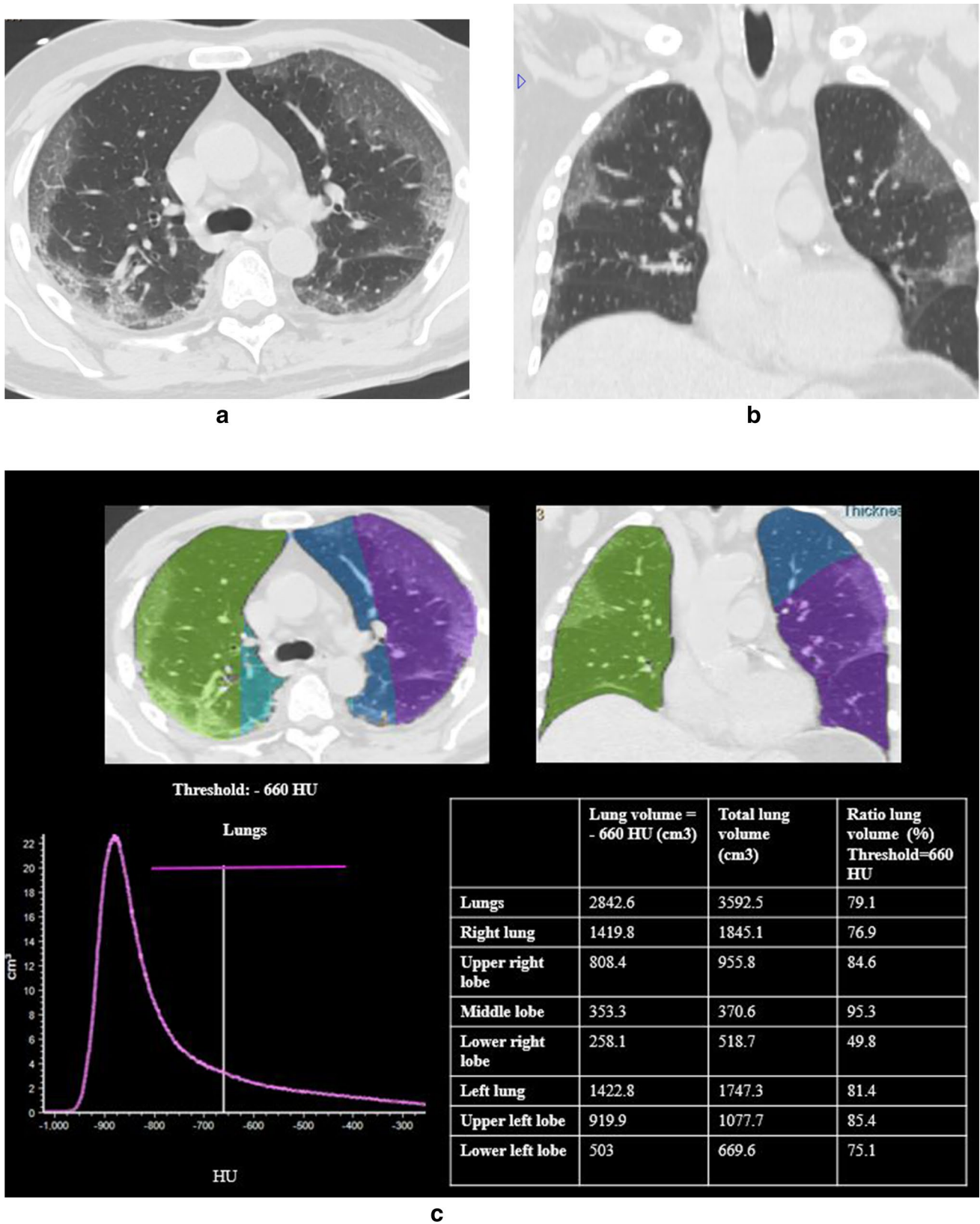
Fig. 4 Sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV) and area under the ROC curve (AUC) for statistically significant features. Colored bars allow a visual comparison of the achieved performance (red for performance measures mainly focusing on positive patients, blue for performance measures mainly focusing on negative patients, yellow for performance measures balancing the performance on positive and negative patients)

Table 5 Other confirmed infections in COVID-19-positive patients and COVID-19-negative patients at second test

Other infections	COVID-19 positive at second test	COVID-19 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
Stenotrophomonas	0\20	2\48
Unknown etiology	0\20	12\48

For each of the observed infections, we report the observed number/total number of COVID-19-positive (20) or COVID-19-negative (48) patients at the second test

or bacterial pneumonia and other lung diseases (vasculitis, dermatomyositis and organizing pneumonia) [27–30].

In a cluster or community transmission scenario, as seen in Northern Italy, when RT-PCR COVID-19 testing is not available or negative, some false-positive cases may be acceptable. A standardized conclusion of a radiological report in terms of suspected COVID-19 pneumonia, pneumonia and negative CT could speed up the diagnostic path of patients, suggesting to clinicians to maintain the patient in isolation, to repeat RT-PCR test or to make a differential diagnosis with other lung infections or other lung diseases.

We evaluated chest CT considering established imaging features that are considered typical of COVID-19 pneumonia [7–10, 20], classifying lung patterns in suspected COVID-19 pneumonia, non-COVID-19 pneumonia and negative CT [31].

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).

The presence of these features at first CT examination could be used as an imaging biomarker to select patients who need a second RT-PCR test (BAL or repeated naso-pharyngeal swab every 48–72 h until persistently negative) in cluster or community transmission scenarios even if it would not be beneficial in a low-prevalence region [24]

In consideration of the rapidly spreading epidemic of COVID-19, in cluster or community transmission scenarios, the early identification of any suspicious case is helpful in order to isolate the patients, administer appropriate treatment and control the emergency disease.

Further studies are needed to evaluate the cost-effectiveness of CT, the benefit–risk ratio of radiation exposure in this condition, and to confirm the diagnostic performance of our imaging criteria in the early identification of RT-PCR false-negative patients.

We believe that the negative COVID-19 patients confirmed by BAL or repeated naso-oropharyngeal swab results, in the presence of a radiological pattern suggestive of COVID-19 pneumonia without other lung infection or disease, should be watched and in the future serological tests could help to confirm the final diagnosis.

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, negative RT-PCR test with positive CT features should be highly suggestive of COVID-19 in a cluster or community transmission scenarios, but it would not be beneficial in a low-prevalence region.

CT could speed up the diagnostic path of patients when RT-PCR COVID-19 testing is not available or negative, suggesting to clinicians to maintain the patient in isolation, to repeat RT-PCR test or to make a differential diagnosis with other lung infections or other lung diseases.

Compliance with ethical standards

Conflict of interest The authors declare there are no known competing interests associated with this publication.

Ethics approval This study was approved by our Ethical Committee.

Human and animal rights Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Informed consent was waived because of the retrospective nature of the study and the use of anonymous clinical data.

Consent for publication Informed consent was waived because of the retrospective nature of the study and the use of anonymous clinical data.

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