Incidental findings suggestive of COVID-19 pneumonia in oncological patients undergoing 18F-FDG PET/CT studies: association between metabolic and structural lung changes.

**Short title.** PET and CT lung changes on COVID-19.

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ABSTRACT

Although the novel coronavirus disease 2019 (COVID-19) can present as non-specific clinical forms, subclinical cases represent an important route of transmission and a significant source of mortality, mainly in high-risk subpopulations such as cancer patients. A deeper knowledge about the shift in cellular metabolism of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected cells could provide new insights about its pathogenic and host response and help to diagnose pulmonary involvement. We explored the association between metabolic and structural changes of lung parenchyma in asymptomatic cancer patients with suspected COVID-19 pneumonia, as a potential added diagnostic value of fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography-computed tomography (PET/CT) scans in this subpopulation.

Methods. Within the period of February 19 and May 29, 2020 ¹⁸F-FDG PET/CT studies were reviewed to identify those cancer patients with suggestive incidental findings of COVID-19 pneumonia. PET studies were interpreted through qualitative (visual) and semiquantitative analysis (measurement of maximum standardized uptake value, SUVmax) evaluating lung findings. Several characteristic signs of COVID-19 pneumonia on computed tomography (CT) were described as COVID-19 Reporting and Data System (CO-RADS) categories (1-6). After comparing SUVmax values of pulmonary infiltrates among different CO-RADS categories, we explored the best potential cut-off values of pulmonary SUVmax against CO-RADS categories as "gold standard" result to discard the diagnosis of COVID-19 pneumonia.

Results. CT signs classified as CO-RADS category 5 or 6 were found in 16/41 (39%) oncological patients derived to multimodal PET/CT imaging. SUVmax was higher in patients with CO-RADS 5 and 6 vs. 4 (6.17±0.82 vs. 3.78±0.50, p=0.04) and vs. 2 and 3 categories (3.59±0.41, p=0.01). A specificity of 93.8% (IC 95%: 71.7-99.7%) and an accuracy of 92.9% were obtained when combining a CO-RADS score 5-6 with a SUVmax of 2.45 in pulmonary infiltrates.

Conclusions. In asymptomatic cancer patients, the metabolic activity in lung infiltrates is closely associated with several combined tomographic changes characteristic of COVID-19 pneumonia. Multimodal ¹⁸F-FDG PET/CT imaging could provide additional information during early diagnosis in selected predisposed patients during pandemic. The prognostic implications of simultaneous radiological and molecular findings in cancer and other high-risk subpopulations for COVID-19 pneumonia deserve further evaluation in prospective researches.

Keywords: COVID-19, pneumonia, lung, cancer, ¹⁸F-FDG PET/CT.
INTRODUCTION

Since December 2019, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads quickly worldwide from a cluster of pneumonia in Wuhan, China. Although the novel coronavirus disease 2019 (COVID-19) can present as different, non-specific clinical forms, subclinical cases represent an important route of transmission and a significant source of morbidity and mortality.

While COVID-19 is usually confirmed by reverse transcription-polymerase chain reaction (rRT-PCR) in respiratory tract specimens, some imaging techniques may strongly suggest the diagnosis until laboratory results are available. In addition, many concerns have been raised about the low sensitivity of rRT-PCR tests (1). In this scenario, chest computed tomography (CT) has positioned as the most useful, non-invasive tool in the diagnosis of COVID-19 pneumonia. Moreover, some CT patterns observed in patients with COVID-19 pneumonia during pandemic, were even more sensitive than rRT-PCR. Despite the limitations of rRT-PCR, it is considered the best diagnostic tool to date.

Several clinical features of the novel infection are particularly challenging in cancer patients. In fact, cancer is a high-risk factor for viral infections, and oncological patients usually demonstrate an indolent clinical course and a high case fatality rate (2,3). Recent observational studies confirmed the higher risk of this subpopulation during COVID-19 outbreaks (3,4). Unfortunately, the differentiation among several respiratory virus and other causes of pneumonitis is really difficult in this subpopulation (5). So, the rate of suspected infection in asymptomatic predisposed patients should consider the updated epidemiological data, the risk of infection and an individualized analytical, imaging and rRT-PCR or gene sequencing assessment.

Few reports and small case series of cancer patients documented the presence of incidental lung changes with fluorine-18 fluorodeoxyglucose (18F-FDG) uptake in positron emission tomography-computed tomography (PET/CT) studies suggestive of COVID-19 pneumonia. This data suggests a potential contribution of this technique in the differential diagnosis of complex or asymptomatic presentations of COVID-19 (6-10). In addition, a deeper knowledge about the shift in cellular metabolism of SARS-CoV-2 infected cells could provide new insights about pathogenic of
viral infection and host response and help to diagnose the pulmonary and distant involvement in selected cases. However, a detailed characterization of combined clinical data, radiological and molecular lung findings in cancer patients with COVID-19 pneumonia is still lacking. With our experience we aimed to explore the association between metabolic and structural changes observed in lung parenchyma of asymptomatic cancer patients with suspected COVID-19 pneumonia, as a potential added diagnostic value of $^{18}$F-FDG PET/CT in this predisposed subpopulation.

**MATERIAL AND METHODS**

**Study Population**

1065 PET/CT scans performed from February 19 to May 29, 2020 were analyzed. All subjects studied through non $^{18}$F-FDG radiotracer or with non-oncological indications, localized brain studies (functional/tumoral brain PET) and patients with suggestive symptoms of respiratory tract infection (e.g.: fever, cough, dyspnoea, sneezing) were excluded, a total of 967 oncologic $^{18}$F-FDG PET/CT were included. This last exclusion criteria was the result of the updated European Association of Nuclear Medicine recommendations, in which all the subjects derived from PET/CT were questioned to detect any symptoms suggestive of COVID-19 infection or any personal contact with a confirmed case during the last 12-48 hours (11). The statement of Helsinki declaration for clinical research in humans was respected. The research was approved by the local Ethical Committee and due to its retrospective design during COVID-19 pandemic in Spain, the need for an individual informed consent was waived (IRB no. 20/524-E).

**Clinical and Analytical Data**

We reviewed the data obtained from $^{18}$F-FDG PET/CT studies to identify those patients with suggestive incidental findings of COVID-19 pneumonia, including clinical and demographics variables, oncologic indication, biochemical profile and follow-up by clinical and imaging techniques after PET/CT.

**PET/CT Imaging**

A usual preparation protocol for $^{18}$F-FDG PET/CT was followed, acquiring the images after 6 hours fasting in non-diabetics or 4 hours in diabetic patients with blood glucose <200 mg/dl. All patients remained at rest during 40-60 minutes after intravenous administration of $^{18}$F-FDG (5MBq/kg). All studies were acquired following the
European Association of Nuclear Medicine guidelines in a Siemens Biograph 6 True Point PET/CT multimodal equipment, with 6 ring detector CT, performing a diagnostic CT (Topogram Dose Modulation System, CARE Dose4D) slice thickness: 5 mm, reconstruction interval: 3 mm. A first inspirational chest CT study was reconstructed as 2.5 mm slices, 60 mAs and 110 KV, with a tube rotation time of 0.6 s and a pitch of 1.2. Then, another body CT study was performed from the base of the skull to the midthigh in cranio-caudal direction, during free breathing. In patients with no contrast CT obtained during last month, and in the absence of contraindications as iodine allergy or kidney failure, an intravenous dose of iodinated contrast (130 ml of Iohexol, Omnipaque®, 300mgI/ml) was administered. A total of 782/967 18F-FDG PET/CT were performed after iodinated contrast administration. Finally, PET study was performed in the same locations as CT study. The acquisition time was 3 minutes per bed (stretcher position). Data obtained from PET/CT were merged into a dedicated workstation using Syngo™ software system (Siemens Medical Imaging, Germany). Regions of interest were manually placed, and maximum standardized uptake values (SUVmax) were recorded in lung parenchyma.

**Image Interpretation and Clinical Referral after PET/CT**

PET/CT scans were reviewed by at least a nuclear medicine physician and a radiologist, obtaining consensus for the final interpretation of each study. All PET/CT studies were interpreted in terms of qualitative (changes were interpreted as positive when the pulmonary infiltrates showed tracer uptake greater than normal lung activity) and semiquantitative (SUVmax) analysis of pulmonary findings. The presence of several diagnostic features in chest CT like opacities pattern, bilateralism, lobe involvement, multi-segmentation, extension, proximity to visceral pleura and fissures, "crazy paving" pattern, hilair lymphadenopathies and pleural effusion were reported by an expert radiologist. Then, the tomographic changes were combined and characterized applying the COVID-19 Reporting and Data System (CO-RADS) criteria, categorized from 0 to 6 (12,13). In line with local and regional recommendations, all patients with CT findings suggesting COVID-19 pneumonia, categorized as CO-RADS 4 or 5 on PET/CT were derived to the emergency department, immediately after contacting the referring oncology team. All the indications of hospital incoming or home isolation, preventive measures, and clinical management, were performed by the emergency and oncology team. In patients categorized as CO-RADS 1 to 3, PET/CT result was referred to the treating oncologist as usually.
COVID-19 Diagnosis in the Real-life Setting

Diagnostic rRT-PCR was obtained from upper or lower respiratory specimens. When available, we included one or more serologic criteria as a surrogate of rRT-PCR. This essay is a plate-based assay designed for detecting antibodies, obtained through enzyme-linked immunosorbent assay from venous peripheral. A “confirmed case” of COVID-19 was defined as patients exhibiting CO-RADS 5 or 6 category (CO-RADS 5 with or without genetic or serologic confirmation by rRT-PCR or enzyme-linked immunosorbent assay techniques, respectively), in the absence of clinical or radiologic findings suggesting other causes of lung infiltrates related to cancer (radiant or cyostatic pneumonitis, tumoral lymphadenopathies, carcinomatous lymphangitis, secondary or newly primary tumoral lesions) (12). These relevant differential diagnoses were defined by consensus involving at least a radiologist and a nuclear medicine physician. Due to the design and the previously reported false negative rate of rRT-PCR, we declare that the diagnosis could not be confirmed in all subjects of our study sample (14,15).

Statistics

Normality of data was tested through Kolmogorov-Smirnoff test. Continuous data was presented as mean±standard deviation or median±interquartile range (25-75), when appropriate, and discrete or categorical variables as frequencies (n,%). Discrete variables were compared through Fisher exact test. A one-way analysis of variance followed by posthoc test (Tukey) was applied to compare the SUVmax values among cancer patients with different combined tomographic signs included in CO-RADS categories, grouped as: 5 and 6 vs. 4 vs. 2 and 3. A second analysis was aimed to dichotomize the categorization of chest CT diagnosis as a “high/very high suspicion” pattern (group I: CO-RADS 5 and 6) vs. an “indeterminate/low suspicion” pattern of COVID-19 pneumonia (group II: CO-RADS 2, 3 and 4). An unpaired “t” test was applied to compare the pulmonary SUVmax between both groups. Considering the quasi-optimal sensitivity obtained with several combined characteristic findings on chest CT expressed as CO-RADS 5, we constructed ROC curves to explore the best potential cut-off value of pulmonary SUVmax against these structural criteria as a gold standard result for diagnosis of COVID-19 pneumonia, that is, as a second, successive, blind step added to chest CT interpretation (1,12). With this purpose, the sensitivity, specificity, likelihood ratio and accuracy were calculated for different cut-off values. As the ratio of patients with/without the disease does not reflect the true prevalence of the illness, we used the prevalence method to estimate accuracies for each cut-off. Accuracy was calculated considering a local prevalence of COVID-19 pneumonia of 1.6% during the study period. A p-value <0.05.
was considered as significant (two tailed). All the analysis and built-in graphics were performed applying GraphPad Prism software (version 9.0.0).

RESULTS

A total of 41 patients from 967 studies derived to 18F-FDG PET/CT for oncological indications showed pulmonary infiltrates on CT during the study period, representing a frequency of pulmonary infiltrates of 4.2% (41/967).

Lung (n=8), head and neck tumors (n=7) and breast cancer (n=6) were the most frequent oncological indications for 18F-FDG PET/CT, representing 51% (21/41) of patients. Serum biochemical profile was available in 20/41 patients; most of them with pulmonary infiltrates categorized as CO-RADS 5 on CT (p=0.004). Clinical and analytical characterization of the study population is provided in Table 1.

CT signs classified as CO-RADS category 5 or 6 were found in 39% (16/41) of our sample. Almost all of this group of patients (15/16, 94%) had ground glass opacities on CT. Infiltrates were bilateral in 12 patients of this group and peripherally distributed in 10 of them. The presence of subpleural fibrous bands was also frequent (9/16, 56%). A characteristic "crazy paving" pattern was detected in 25% (4/16) of the patients. In contrast, no lymphadenopathies or pleural effusion was observed in any subject of this group. These lung changes are illustrated in two clinical cases (Figures 1 and 2).

Tests for COVID-19 were available in 20 patients; results were positive in 13 and negative in 7 patients. CO-RADS categories were distributed as follows: 6: 24% (10/41), 5: 14% (6/41), 4: 27% (11/41), 3: 24% (10/41) and 2: 10% (4/41). As a result of qualitative analysis, the lung activity was interpreted as "positive" in 40 patients. After multiple comparisons of SUVmax among different CO-RADS categories, a higher SUVmax was found in patients with CO-RADS 5 and 6 vs. 4 (6.17±0.82 vs. 3.78±0.50, p=0.04) and vs. CO-RADS 2 and 3 categories (3.59±0.41, p=0.01, Figure 3). After aggregating tomographic categories, SUVmax values obtained in group I were higher than those of group II (6.17±0.82 vs. 3.67 ±0.31, p=0.002) (Figure 3).
The area under the curve (AUC) obtained for different cut-off values of SUVmax was 0.73 (IC 95%: 0.56-0.90, p=0.015, Figure 4). The diagnostic yield aimed to discard the diagnosis, estimated by specificity and likelihood ratio of different cut-off values of SUVmax against CO-RADS 5 and 6 as a gold standard result are presented in Table 2. A SUVmax cut-off value of 3.10 obtain a specificity of at least 75.0%. The best specificity (93.8%, IC 95%: 71.7-99.7%) and higher likelihood ratio and accuracy were obtained when combining a CO-RADS score 5 and 6 with a SUVmax of 2.45 in pulmonary infiltrates.

A subtotal of 35/41 patients with pulmonary infiltrates on 18F-FDG studies were followed by imaging techniques during the next weeks after PET/CT (8 days-8 months). Pulmonary findings improved/resolved in 31/35 patients, worsened in 2/35 patients and evolved to post-COVID-19 sequelae in 2/35 cases. Five patients (5/41) referred from other centers were lost during follow-up. Only one patient (1/41), a 78-year-old man with urothelial cancer without signs of recurrence on PET/CT died 8 days after PET/CT study as a result of severe respiratory failure. In this fatal case, COVID-19 pneumonia was confirmed by rRT-PCR, pulmonary changes were classified as CO-RADS 5 on CT and SUVmax was 6.0 on molecular imaging.

DISCUSSION

Incidental changes suggesting COVID-19 pneumonia in chest CT were founded in 4.1% of cancer patients derived to 18F-FDG PET/CT in our centre, a lower proportion than previously reported (7,1-9.2%) (7,8,16). These heterogeneous results could be explained by the health care facilities and policies assumed in different medical centres and countries, the time-dependent transmissibility of the virus and/or other factors related with the study sample (4,11,17).

Although the diagnostic potential of the metabolic activity observed in pulmonary infiltrates of suggestive or confirmed COVID-19 pneumonia on PET/CT studies has been described in some recent researches, the correlation between tomographic structural changes (CO-RADS system) and metabolic activity (SUVmax) of the lung parenchyma had not been evaluated in detail until now (6-10,16-21). Our preliminary results could provide a new
perspective on the pathophysiology of SARS2-CoV-2 lung infection and even redefine the best diagnostic imaging criteria in several patient subpopulations.

The performance of chest CT for the diagnosis of COVID-19 pneumonia could be even better when applying several combined findings as CO-RADS (22). However, the validation of CO-RADS scale has been carried out mainly in patients with moderate/severe symptoms and a minor incidence of cancer (21%) (18). The specificity obtained through our successive, diagnostic design ranged from 81.2-95.5% considering SUVmax cut-off values 2.25-3.10. Longitudinal investigation has confirmed that a high proportion of asymptomatic patients with COVID-19 pneumonia manifest symptoms usually during next days and weeks (23). A higher SUVmax obtained in those CT findings described as more specific for COVID-19 pneumonia (9,22) represents a new tool about the predictive value of different CO-RADS categories and also suggest its clinical contribution to discard this viral pneumonia in cancer patients, even before the appearance of symptoms.

The methodological approach of this study was aimed to explore if the SUVmax value obtained in new pulmonary infiltrates could contribute to discard the diagnosis of COVID-19 pneumonia, that is, improving the specificity obtained through isolated structural changes of chest CT. Not surprisingly, the best specificity was obtained with a SUVmax cut-off of 2.25-2.55, a value that has been similarly reported as an indicator of benign etiology. This empirical cut-off value and the relationship demonstrated between higher SUVmax-more suspicious CO-RADS category are coherent with observational researches of other non-malignant pulmonary process (24). However, we confirmed that a higher SUVmax were predominately observed in the presence of several tomographic signs of COVID-19 pneumonia (Figure 3). In addition to its diagnostic contributions, the close correlation between structural and metabolic findings could stimulate future research on the pathophysiology of COVID-19 lung injury in predisposed subjects for better characterizing the local inflammatory component and its possible changes in response to new therapies.

However, the variation of SUVmax observed in lung changes related to COVID-19 pneumonia could also be influenced by several factors such as patient weight, motion artifacts, blood glucose levels, dose extravasation, accuracy of dose calibration and time between injection and imaging. Previous reports of certain inflammatory
pneumonias found that lung areas with consolidation patterns are associated with higher SUVmax values compared to areas with ground glass opacities patterns. Histopathological examinations have revealed that the number of CD45+ cells and CD8+ T lymphocytes in parenchymal lung lesions is positively correlated with SUVmax (25). As it is well known that there are non-cellular components in ground glass opacities areas (particularly in fluid-filled intraalveolar regions), SUVmax is lower in this pulmonary pattern. This supports the hypothesis that the highest CO-RADS, the highest SUVmax, as the CO-RADS 5 category includes patterns of lung consolidation, while the CO-RADS 3 to 5 categories include ground glass opacities patterns (12,25,26). In addition, the pulmonary findings related to COVID-19 pneumonia may vary according to the phase of alveolar damage. In the end-stage with fully established fibrosis, destruction of the lung parenchyma is described, which could justify the lower SUVmax values obtained in presence of lung fibrosis (CO-RADS 1) (12,26). Finally, the pulmonary findings in COVID-19 are not limited to a simple infiltrate of infectious and inflammatory cells, but to the possible appearance of various damages related to vessels, such as capillary leaks and thrombosis (26,27). Although auspicious, the true and complete diagnostic value of different individual CT findings combined with local SUVmax detected by 18F-FDG PET/CT should be explored in larger, multicenter experiences.

Several lung inflammatory diseases can be characterized by similar molecular findings as COVID-19 pneumonia in cancer patients (24). As a consequence, SARS-CoV-2 infection always needs to be distinguished from other viral, bacterial/fungal and other infrequent pneumonias, non-infectious diseases like pulmonary vasculitis, dermatomyositis, organizing pneumonia and post-therapeutic changes. Finally, some patients with viral pneumonia may test positive to more than one virus, and the potential lethality of a SARS-CoV-2- influenza virus co-infection should not be ignored. As we considered multiple CT findings and experts opinions to diagnose COVID-19 pneumonia during a local outbreak, and in the absence of other infectious screening and one/more genetic testing in all patients, our results should be interpreted cautiously, generating a plausible hypothesis about early diagnostic value of PET/CT in cancer patients (28).

Our results also support that all nuclear medicine physicians should pay special attention to incidental findings suggesting pneumonia in 18F-FDG PET/CT studies, and act as soon as possible (29). During COVID-19 outbreak in Spain, all nuclear medicine departments followed the safety and prevention protocols provided by the
European Association of Nuclear Medicine, in a collective effort to allow for safer diagnosis and treatment procedures (11). Importantly, 18F-FDG PET/CT is a more complex study than chest CT, leading a possible increased risk of viral spreading due to the longer time of the whole procedure. So, the probability to study asymptomatic patients with COVID-19 infection through several usual nuclear medicine procedures like 18F-FDG PET/CT is not negligible (29). On the other hand, the oncology team needed to weigh the risks of death and morbidity from COVID-19 against the benefits of several therapies. Obtaining more detailed data through PET/CT could have a double impact related with the risk of spreading the infection and expected benefits of cancer therapy. This complex critical scenario requires an adequate balance that must be individualized in each clinical context.

Main limitation of our experience is related to the small real-life sample of cancer patients with suspected COVID-19 pneumonia studied in a single center. Secondly, the time since infection is not known, preventing the real impact of early diagnosis during the course of infection in predisposed patients. Third, only one examiner interpreted CT images, and inter-rater variability in each CO-RADS category was not evaluated (22). Finally, the size of reference bias was not estimated.

CONCLUSIONS

In asymptomatic cancer patients, SUVmax of lung parenchyma infiltrates on 18F-FDG PET/CT studies is closely associated with several tomographic changes characteristic of COVID-19 pneumonia. Multimodal 18F-FDG PET/CT imaging could provide additional information during the diagnosis of COVID-19 in selected patients, even in early stages of the disease. Next prospective experiences are required to define the prognostic value of combining radiological and molecular findings in cancer and other high-risk subpopulations for COVID-19 pneumonia.

DISCLOSURE

Publication charges were funded by IdISSC. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

Not applicable.
KEY POINTS

QUESTION: What is the association between metabolic and structural changes of lung parenchyma in asymptomatic cancer patients with suspected COVID-19 pneumonia?

PERTINENT FINDINGS: SUVmax of lung parenchyma infiltrates is closely associated with several tomographic changes characteristic of COVID-19 pneumonia (CO-RADS) on asymptomatic cancer patients undergoing 18F-FDG PET/CT.

IMPLICATIONS FOR PATIENT CARE: 18F-FDG PET/CT may provide additional information about early diagnosis of COVID-19 pneumonia in cancer patients during pandemic.
REFERENCES


### Table 1. Clinical, oncological and biochemical characterization of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>GROUP I (n=16)*</th>
<th>GROUP II (n=25)†</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.8±13.5</td>
<td>64.7±14.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Male sex (n,%)</td>
<td>15 (60.0)</td>
<td>7 (43.8)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>ONCOLOGICAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer staging (%)</td>
<td>5 (12.2)</td>
<td>7 (17.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>rt-PCR or serologic confirmation (n,%)‡</td>
<td>10 (24.4)</td>
<td>3 (7.3)</td>
<td>0.0014</td>
</tr>
<tr>
<td><strong>BIOCHEMICAL§</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum C reactive protein (mg/ml)</td>
<td>7.5±8.7</td>
<td>4.4±8.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Lymphocytes blood count (per mm³)</td>
<td>1.4±0.7</td>
<td>1.2±0.6</td>
<td>0.44</td>
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<tr>
<td>Serum alanine aminotransferase (mg/ml)</td>
<td>18.6±6.5</td>
<td>19.3±4.8</td>
<td>0.82</td>
</tr>
<tr>
<td>Serum aspartate aminotransferase (mg/ml)</td>
<td>27.6±12.8</td>
<td>22.3±6.3</td>
<td>0.33</td>
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<tr>
<td>Serum lactate dehydrogenase (mg/ml)</td>
<td>586.1±204.6</td>
<td>473.0±163.8</td>
<td>0.22</td>
</tr>
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</table>

*Group I = CO-RADS 5 and 6.

†Group II = CO-RADS 2, 3 and 4.

‡One patient with diagnosis of COVID-19 infection was confirmed by serologic IgG test (enzyme-linked immunosorbent assay).

§Analytics were available in patients derived to the emergency department with high/very high suspicious based on CO-RADS categories.
Table 2. Potential usefulness of different cut-off values of $^{18}$F/FDG PET/CT SUVmax to confirm and discard the tomographic diagnosis of COVID-19.

<table>
<thead>
<tr>
<th>SUVmax cut-off value</th>
<th>Sensitivity (%)</th>
<th>IC 95% (%)</th>
<th>Specificity (%)</th>
<th>IC 95% (%)</th>
<th>LR</th>
<th>Accuracy (%)</th>
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<tr>
<td>&lt;2.45</td>
<td>24.0</td>
<td>11.5-43.4</td>
<td>93.8</td>
<td>71.7-99.7</td>
<td>3.8</td>
<td>92.9</td>
</tr>
<tr>
<td>&lt;2.55</td>
<td>24.0</td>
<td>11.5-43.4</td>
<td>87.5</td>
<td>64.0-97.8</td>
<td>1.9</td>
<td>86.7</td>
</tr>
<tr>
<td>&lt;2.85</td>
<td>32.0</td>
<td>17.2-51.6</td>
<td>81.3</td>
<td>57.0-93.4</td>
<td>1.7</td>
<td>80.7</td>
</tr>
<tr>
<td>&lt;3.10</td>
<td>36.0</td>
<td>20.3-55.5</td>
<td>75.0</td>
<td>50.5-89.8</td>
<td>1.4</td>
<td>74.5</td>
</tr>
</tbody>
</table>

LR = likelihood ratio.
Figure 1. An 86-year-old woman with a second primary lung tumour (B, C, blue arrow) referred to PET/CT to assess therapeutic response. MIP (A) and axial sections with lung window (B) and fusion images (C) showed several pulmonary consolidations located mainly in right inferior lobe (red arrows, CO-RADS 5) with increased FDG uptake (SUVmax 4.6). rRT-PCR was positive for COVID-19.
Figure 2. Staging PET/CT of a 43-year-old woman with breast cancer (A, blue arrow). MIP (A) and axial sections with lung window (B) and fusion (C) shows bilateral ground glass pulmonary infiltrates (red arrows), some of them with pseudonodular morphology, located in both lower lobes and left middle lobe, with a diffuse/peripheral distribution (SUVmax 7.8). Early rRT-PCR obtained in the emergency department was negative for COVID-19 and a second test was not available.
Figure 3. Association of molecular and structural findings observed in multimodal imaging.

Comparison of SUVmax among cancer patients with different CO-RADS categories.
Figure 4. ROC curve of SUVmax to detect COVID-19 pneumonia on the basis of structural tomographic diagnosis (CO-RADS 5 and 6).
Graphical Abstract
Flowchart of the study

Consecutive PET-CT scans from February 19 to May 29, 2020
\( (n = 1065) \)

Scans excluded
\( (n = 98) \)
- Non \(^{18}\)F-FDG radiotracer \( (n = 12) \)
- Localized brain studies \( (n = 18) \)
- Infectious/inflammatory indications \( (n = 24) \)
- Other non-oncological indications \( (n = 44) \)

Oncological \(^{18}\)F-FDG PET-CT scans
\( (n = 967) \)

Patients without pulmonary infiltrates
\( (n = 926) \)

Patients with pulmonary infiltrates
\( (n = 41) \)

CO-RADS 5 and 6.
\( (n = 16) \)
- SUVmax \( 6.17 \pm 0.82 \)
- COVID-19 test
  - Positive \( (n = 10) \)
  - Negative \( (n = 1) \)
  - Not available \( (n = 5) \)

CO-RADS 4.
\( (n = 11) \)
- SUVmax \( 3.78 \pm 0.50 \)
- COVID-19 test
  - Positive \( (n = 2) \)
  - Negative \( (n = 1) \)
  - Not available \( (n = 8) \)

CO-RADS 2 and 3.
\( (n = 14) \)
- SUVmax \( 3.59 \pm 0.41 \)
- COVID-19 test
  - Positive \( (n = 1) \)
  - Negative \( (n = 5) \)
  - Not available \( (n = 8) \)

Scans excluded
\( (n = 98) \)
- Non \(^{18}\)F-FDG radiotracer \( (n = 12) \)
- Localized brain studies \( (n = 18) \)
- Infectious/inflammatory indications \( (n = 24) \)
- Other non-oncological indications \( (n = 44) \)