



Increased incidence of interstitial pneumonia detected on [¹⁸F]-FDG-PET/CT in asymptomatic cancer patients during COVID-19 pandemic in Lombardy: a casualty or COVID-19 infection?

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Abstract

Purpose The study aimed to compare the incidence of interstitial pneumonia on [¹⁸F]-FDG PET/CT scans between two 6-month periods: (a) the COVID-19 pandemic peak and (b) control period. Secondly, we compared the incidence of interstitial pneumonia on [¹⁸F]-FDG PET/CT and epidemiological data from the regional registry of COVID-19 cases. Additionally, imaging findings and the intensity of [¹⁸F]-FDG PET/CT uptake in terms of maximum standardized uptake value (SUV_{max}) were compared.

Methods We retrospectively analyzed [¹⁸F]-FDG PET/CT scans performed in cancer patients referred to nuclear medicine of Humanitas Gavazzeni in Bergamo from December 2019 to May 2020 and from December 2018 to May 2019. The per month incidence of interstitial pneumonia at imaging and the epidemiological data were assessed. To evaluate the differences between the two symmetric groups (period of COVID-19 pandemic and control), the stratified Cochran–Mantel–Haenszel test was used. Chi-square test or Fisher’s exact test and *t* test or Wilcoxon test were performed to compare the distributions of categorical and continuous variables, respectively.

Results Overall, 1298 patients were included in the study. The two cohorts—COVID-19 pandemic (*n* = 575) and control (*n* = 723)—did not statistically differ in terms of age, disease, or scan indication (*p* > 0.05). Signs of interstitial pneumonia were observed in 24 (4.2%) and 14 patients (1.9%) in the COVID-19 period and the control period, respectively, with a statistically significant difference (*p* = 0.013). The level of statistical significance improved further when the period from January to May was considered, with a peak in March (7/83 patients, 8.4% vs 3/134 patients, 2.2%, *p* = 0.001). The curve of interstitial pneumonia diagnosis overlapped with the COVID-19 incidence in the area of Lombardy (Spearman correlation index was equal to 1). Imaging data did not differ among the two cohorts.

Conclusions Significant increase of interstitial lung alterations at [¹⁸F]-FDG PET/CT has been demonstrated during the COVID-19 pandemic. Additionally, the incidence curve of imaging abnormalities resulted in resembling the epidemiological data of the general population. These data support the rationale to adopt [¹⁸F]-FDG PET/CT as sentinel modality to identify suspicious COVID-19 cases to be referred for additional confirmatory testing. Nuclear medicine physicians and staff should continue active surveillance of interstitial pneumonia findings, especially when new infection peak is expected.

Keywords SARS-CoV-2 · COVID-19 · Interstitial pneumonia · [¹⁸F]-FDG-PET/CT · Lung consolidations · Ground-glass opacities

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Introduction

Firstly identified in China at the end of 2019, the severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] [1] has had a rapid spread, which resulted in a significant impact on the health of the world population [2].

Worldwide, 11,500,302 COVID-19 cases as of July 07, 2020 [3] have been registered, being Italy as one of the most affected countries [4]. Italian data from the National Healthcare (Istituto Superiore di Sanità-ISS) platform as of July 07, 2020 reported 241,819 cases (0.4% of the population) diagnosed by the regional reference laboratories as positive for SARS-CoV-2. The period of maximum incidence in Italy has been in the last 10 days of March with the peak of 6557 new cases on March 21, 2020 in one single day [5].

Lombardy is the Italian region most interested by the outbreak with 94,527 confirmed cases (0.9% of the population), and the province of Bergamo was one of the areas with the highest spread of infection with 14,523 cases (1.3%) [5, 6]. From February 2020 to May 2020, 837 patients were admitted for COVID-19 infection in Humanitas Gavazzeni Hospital.

The diagnosis of COVID-19-related interstitial pneumonia is generally based on exposure history, clinical symptoms, blood results, and biochemical tests. However, a proportion of infected patients can be asymptomatic. Definitive diagnosis needs nasopharyngeal swabs for SARS-COV-2 analysis by real-time polymerase chain reaction (RT-PCR) [7]. Imaging such as chest computed tomography (CT) [8, 9] and [¹⁸F]-fluorodeoxyglucose positron emission tomography ([¹⁸F]-FDG PET/CT) [1, 10] can reveal lung involvement [11]. [¹⁸F]-FDG PET/CT has been already described as a tool to provide a diagnosis of interstitial pneumonia [12, 13], which is one of the most common presentation of COVID-19 disease [14]. However, [¹⁸F]-FDG PET/CT findings are not specific for COVID-19 pneumonia. Therefore, COVID-19 infection should be confirmed through further laboratory tests, such as RT-PCR. On the other hand, we incidentally identified several cases of [¹⁸F]-FDG PET/CT findings suspicious for COVID-19-related pneumonia in asymptomatic cases [10, 15]. Therefore, we hypothesized that [¹⁸F]-FDG PET/CT can serve as sentinel modality able to identify COVID-19 pneumonia and to guide further diagnostic procedures. Consequently, we decided to test our hypothesis by pursuing the following aims. Firstly, we aimed at comparing the incidence of interstitial pneumonia on [¹⁸F]-FDG scans between two 6-month periods: (a) the COVID-19 pandemic peak in our region (Lombardy) and (b) control period, in a group of high risk patients, such as patients with cancer. Secondly, we compared the trend of the incidence of interstitial pneumonia on [¹⁸F]-FDG PET/CT and epidemiological data from the regional registry of COVID-19 cases. Additionally, imaging findings and the intensity of [¹⁸F]-FDG PET/CT uptake between the analyzed periods in terms of maximum standardized uptake value (SUVmax) were compared.

Materials and methods

Population

We retrospectively analyzed two series of consecutive patients that performed [¹⁸F]-FDG PET/CT [16] for cancer detection, therapy response evaluation, and follow-up. The first cohort included scans performed during 6 month starting from December 2019 to May 2020, including the COVID19 pandemic; the second cohort was scanned from December 2018 to May 2019, considered as the COVID-19-free control period. Patients with history or symptoms of any infection or inflammatory disease were excluded from the study.

COVID-19 incidence data, and in particular those in the area of Bergamo, were accessed from Lombardy (Italy) registry (Osservatorio della Regione Lombardia) [5].

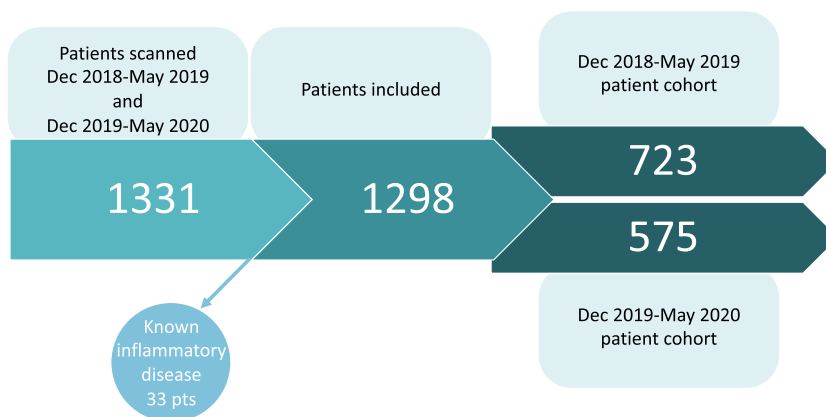
[¹⁸F]-FDG PET/CT analysis

[¹⁸F]-FDG PET/CT studies were performed according to the standard protocols following the EANM guidelines [17] on a Phillips Gemini LXL PET/CT with an integrated 16-slice CT. Being these studies carried out for diagnosis of oncological disease, no specific protocol for the assessment of the lungs was performed. All images were retrospectively evaluated by two experienced nuclear medicine physicians and one expert thoracic radiologist. The diagnosis of highly suspicious viral pneumonia was based on the findings of bilateral pulmonary infiltrates and subpleural pseudo-nodular mixed ground-glass and consolidative lesions [18, 19]. The symmetrical ground-glass opacities located in the posterior basal lobes were considered breath artifacts. During the selection phase, we did not exclude patients affected by conditions that could mimic lung abnormalities such as lung cancer, radiotherapy at thorax, or potentially lung toxic treatments. However, these conditions were considered in the differential diagnosis during image interpretation. SUVmax of the lung abnormalities and lymph nodes was semi-automatically calculated on the Philips Extended Workspace EBW-NM 2.0.2 workstation.

Statistical methods

Continuous variables were described using mean and standard deviation (SD), the median with the first and third quartile (Q1-Q3, interquartile range, IQR), and minimum and maximum values, whereas categorical variables were described using frequencies and percentages. Chi-square test (or Fisher's exact test as appropriate) and *t* test (or Wilcoxon test as appropriate) were performed to compare the distributions of categorical and continuous variable, respectively. To compare the proportions of interstitial pneumonia observed at [¹⁸F]-FDG PET/CT during the COVID-19 pandemic (December 2019 to May 2020) and the control period (December 2018

Fig. 1 Patient selection flowchart



to May 2019), we used a Cochran–Mantel–Haenszel (CMH) test stratified by month when [¹⁸F]-FDG PET/CT was performed. Moreover, the relative risk (RR) of detection of interstitial pneumonia in patients included in COVID-19 period group and the relative 95% confidence interval (95%CI) were provided. The correlation between the curve of [¹⁸F]-FDG PET/CT detection of COVID-19-like interstitial pneumonia and the epidemiologic curve of COVID-19 infection was assessed using the Spearman correlation index. A *p* value <

0.05 was considered to be statistically significant. Analyses were carried out using SAS statistical software (version 9.4).

Results

Overall, 1331 patients performed [¹⁸F]-FDG PET/CT in the COVID-19 period and the COVID-19-free control period. Thirty-three patients with known non-oncological disease

Table 1 Patient population characteristics

	Control period <i>N</i> = 723	COVID-19 period <i>N</i> = 575	Overall <i>N</i> = 1298	<i>p</i> value
Age				0.852
Mean (SD)	65.9 (12.4)	65.8 (12.5)	65.9 (12.4)	
Median (Q1–Q3)	68.3 (57.7–75.1)	67.9 (57.2–75.2)	68.0 (57.5–75.2)	
Min-max	19.5–88.9	20.5–89.4	19.5–89.4	
Sex				0.021
Female	389 (53.8)	346 (60.2)	735 (56.6)	
Male	334 (46.2)	229 (39.8)	563 (43.4)	
Tumor site				0.014
Lung	170 (23.5)	121 (21.0)	291 (22.4)	
Gastrointestinal system	135 (18.7)	115 (20.0)	250 (19.3)	
Breast	115 (15.9)	106 (18.4)	221 (17.0)	
Gynecological apparatus	66 (9.1)	85 (14.8)	151 (11.6)	
Multiple neoplasm	77 (10.7)	45 (7.8)	122 (9.4)	
Head/neck	56 (7.7)	40 (7.0)	96 (7.4)	
Hematological system	32 (4.4)	17 (3.0)	49 (3.8)	
Melanoma and soft tissue	19 (2.6)	14 (2.4)	33 (2.5)	
Urinary tract	19 (2.6)	9 (1.6)	28 (2.2)	
Other	4 (0.6)	8 (1.4)	12 (0.9)	
Unknown	30 (4.1)	15 (2.6)	45 (3.5)	
PET/CT indication				0.537
Staging/restaging	443 (61.3)	335 (58.3)	778 (59.9)	
Treatment response	188 (26.0)	163 (28.3)	351 (27.0)	
Follow-up	92 (12.7)	77 (13.4)	169 (13.0)	

SD standard deviation. Q1–Q3 first and third quartile

Table 2 Interstitial pneumonia incidence on [¹⁸F]FDG PET/CT

	Control period <i>N</i> = 723		COVID-19 period <i>N</i> = 575	
	Interstitial pneumonia		Interstitial pneumonia	
	No	Yes	No	Yes
December–May	709 (98.1)	14 (1.9)	551 (95.8)	24 (4.2)
December	116 (96.7)	4 (3.3)	118 (99.2)	1 (0.8)
January	139 (99.3)	1 (0.7)	103 (96.3)	4 (3.7)
February	114 (98.3)	2 (1.7)	112 (95.7)	5 (4.3)
March	131 (97.8)	3 (2.2)	76 (91.6)	7 (8.4)
April	110 (98.2)	2 (1.8)	60 (95.2)	3 (4.8)
May	99 (98.0)	2 (2.0)	82 (95.3)	4 (4.7)

were excluded. We selected 575 and 723 patients in the COVID-19 period and the COVID-19-free control period, respectively (Fig. 1).

The indication to perform [¹⁸F]-FDG PET/CT was cancer detection in 778/1298 cases (59.9%), therapy response evaluation in 351/1298 patients (27.0%), and follow-up in 169/1298 patients (13.0%). Table 1 reports the patients' characteristics and cohort comparison statistical tests results. In particular, we found that the two cohorts did not statistically differ in terms of age, disease, or scan indication (Table 1).

In the whole population, 162/1298 [¹⁸F]-FDG PET/CT scans showed lung abnormalities that have been interpreted as bacterial infection or radiation-induced consolidations. Eighteen patients affected from lung cancer showed lung abnormalities that were interpreted as cancer-related abnormalities.

Signs of interstitial pneumonia were observed in 24 (4.2%) and 14 patients (1.9%) in the COVID-19 period and the control

period, respectively. Out of the 24 interstitial pneumonia cases, 4 patients have been confirmed to have a SARS-CoV-2 infection using PCR in 3 cases and by antibodies testing in 1 case. The proportion of interstitial pneumonia detected per month on [¹⁸F]-FDG PET/CT is shown in Table 2. Except for December, the proportion of interstitial pneumonia was always higher in COVID-19 period and reached its peak in March (8.4%), corresponding with the greatest difference compared with the control period (8.4% vs 2.2%). A progressive increase from January to March followed by a decrease in April and May is observed for both periods, while in December, a lower proportion is reported in the COVID-19 period (Fig. 2). A statistically significant difference in the occurrence of pneumonia's diagnosis was detected (stratified CMH test, *p* value = 0.013), with a RR for patients in COVID-19 period of 2.20 (95%CI 1.16–4.16). Limiting the analysis to the periods from January to May, the even higher difference was detected (stratified CMH test, *p* value = 0.001; RR 3.11, 95%CI 1.50–6.47).

The incidence of COVID-19 in Bergamo was 0.1‰ in February, 7.79‰ in March, 2.25‰ in April, and 1.84‰ in May. The trend of the curve of [¹⁸F]-FDG PET/CT detection of COVID-19-like interstitial pneumonia is following the epidemiological curve of COVID-19 infection, registered by the Osservatorio della Regione Lombardia in the area of Bergamo (Fig. 3), and the Spearman correlation index is equal to 1.

No clinically significant differences in the patterns of lungs [¹⁸F]-FDG PET/CT findings in the two periods were found, being both [¹⁸F]-FDG PET/CT uptake and CT findings very similar (Table 3). In particular, the intensity of [¹⁸F]-FDG PET/CT uptake, in terms of SUVmax, ranged between 1.9 and 11.3 (median 2.9, IQR 2.5 to 4.3) in the COVID-19 period and between 2.1 and 5.3 (median 3.0, IQR 2.2 to 3.4) in the control period (Wilcoxon test, *p* = 0.562) (Fig. 4 and Fig. 5).

Fig. 2 Interstitial pneumonia detected in the periods December 2018–May 2019 and December 2019–May 2020. Stratified CMH test and Cochran–Mantel–Haenszel test stratified by PET/CT month. 95%CI, 95% confidence interval

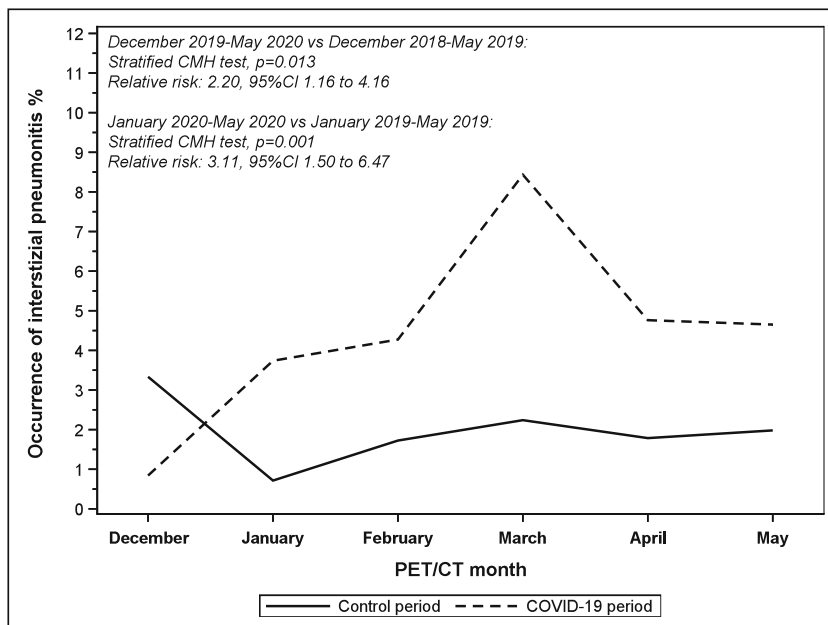


Fig. 3 Comparison between [¹⁸F]FDG PET/CT suggestive for COVID-19 interstitial pneumonia and cases of COVID-19 confirmed in the area of Bergamo

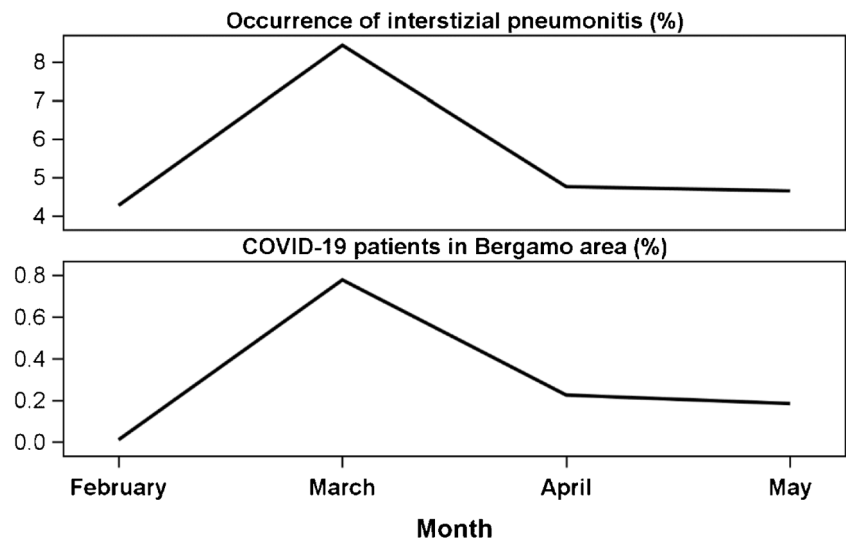


Table 3 Clinical characteristics and [¹⁸F]FDG PET/CT findings in patients with interstitial pneumonia

	Control period <i>N</i> = 14	COVID-19 period <i>N</i> = 24	Overall <i>N</i> = 38	<i>p</i> value
Age				0.916
Mean (SD)	67.9 (12.2)	68.5 (11.9)	68.3 (11.9)	
Median (Q1–Q3)	68.9 (60.8–78.3)	71.7 (60.1–76.7)	70.7 (60.8–77.5)	
Min-max	41.2–84.8	44.9–88.7	41.2–88.7	
Sex				0.101
Female	10 (71.4)	10 (41.7)	20 (52.6)	
Male	4 (28.6)	14 (58.3)	18 (47.4)	
Tumor site				0.388
Lung	3 (21.4)	6 (25.0)	9 (23.7)	
Gastrointestinal system	2 (14.3)	5 (20.8)	7 (18.4)	
Breast	4 (28.6)	4 (16.7)	8 (21.1)	
Gynecological apparatus	0 (0.0)	1 (4.2)	1 (2.6)	
Multiple neoplasm	2 (14.3)	3 (12.5)	5 (13.2)	
Head/neck	0 (0.0)	3 (12.5)	3 (7.9)	
Hematological system	1 (7.1)	0 (0.0)	1 (2.6)	
Melanoma and soft tissue	0 (0.0)	2 (8.3)	2 (5.3)	
Unknown	2 (14.3)	0 (0.0)	2 (5.3)	
PET/CT indication				0.170
Staging/Restaging	10 (71.4)	15 (62.5)	25 (65.8)	
Treatment response	4 (28.6)	4 (16.7)	8 (21.1)	
Follow-up	0 (0.0)	5 (20.8)	5 (13.2)	
[¹⁸ F]FDG PET/CT findings				0.562
SUVmax				
Mean (SD)	3.1 (1.1)	3.6 (1.9)	3.4 (1.7)	
Median (Q1–Q3)	2.9 (2.2–3.4)	3.0 (2.5–4.3)	3.0 (2.3–4.0)	
Min-max	2.1–5.3	1.9–11.3	1.9–11.3	
Laterality				0.081
Monolateral abnormalities	8 (57.1)	6 (25.0)	14 (36.8)	
Bilateral abnormalities	6 (42.9)	18 (75.0)	24 (63.2)	
Alterations				0.684
Ground-glass opacities	12 (85.7)	18 (75.0)	30 (78.9)	
Ground-glass opacities and consolidations	2 (14.3)	6 (25.0)	8 (21.1)	
Enlarged lymph nodes	6 (42.9)	15 (65.2)	21 (56.8)	0.305
Missing	0	1	1	
SUVmax at lymph nodes				0.668
Mean (SD)	4.5 (2.5)	3.9 (2.2)	4.1 (2.3)	
Median (Q1–Q3)	3.5 (3.2–4.1)	3.7 (2.8–4.5)	3.5 (3.0–4.1)	
Min-max	3.1–9.6	1.9–11.2	1.9–11.2	

SD standard deviation; *SUVmax* maximum standardized uptake value

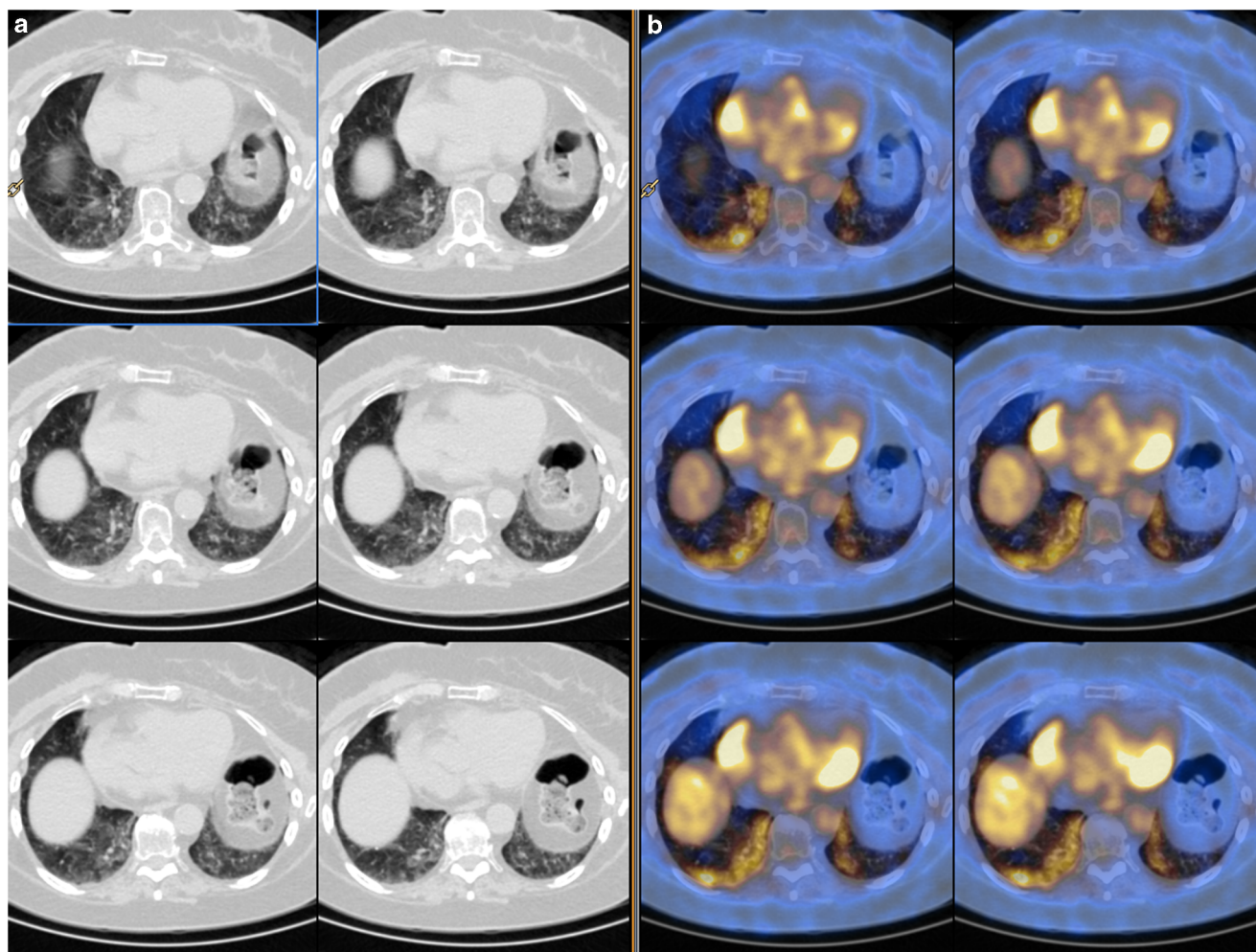


Fig. 4 A 75-year-old patient, affected by breast cancer, who performed the [^{18}F]FDG PET/CT for treatment response in COVID-19-free period. CT (a) (CT axial view) and [^{18}F]FDG PET (b) (fused PET/CT axial view)

were suggestive for interstitial pneumonia. The image shows moderate FDG uptake (SUVmax 3.4) at peripheral ground-glass opacities in lower lung lobes

Discussion

We recorded that during COVID-19 incidence peak in a high prevalence region such as the Bergamo area in Lombardy, Italy, [^{18}F]-FDG PET/CT revealed a higher number of interstitial pneumonia compared with a reference period, with a RR for patients in COVID-19 period of 2.20 (95%CI 1.16–4.16). Additionally, we observed that the occurrence of interstitial pneumonia is in line with the epidemiological COVID-19 data from the regional registry (Osservatorio della Regione Lombardia) (Fig. 2). We hypothesize that such an increase in detection of interstitial pneumonia during the COVID-19 pandemic can be a consequence of the COVID-19 infection. Therefore, our results support the rationale to consider [^{18}F]-FDG PET/CT as a sentinel modality and to trigger SARS-CoV-2 testing. Even if our findings were expected, we

provided the evidence, utilizing proper statistical tests, that FDG PET imaging abnormalities were more frequent during the COVID-19 outbreak. Indeed, our opinion is that a clear demonstration was needed to justify further investigations and improve clinical practice.

Our findings appear partly in contrast with the results reported by Maurea et al. [20]. The authors evaluated the occurrence of lung abnormalities on imaging suspicious or potentially diagnostic for interstitial pneumonia by COVID-19 infection in southern Italy. They found that the percentage of findings suspicious for interstitial pneumonia by COVID-19 infection was significantly higher during the pandemic (February–April 2020) (9%) compared with that found in the corresponding period of 2019 (4%) (χ^2 5.45, p = 0.02). However, clinical data or laboratory tests resulted in negative for SARS-CoV-2

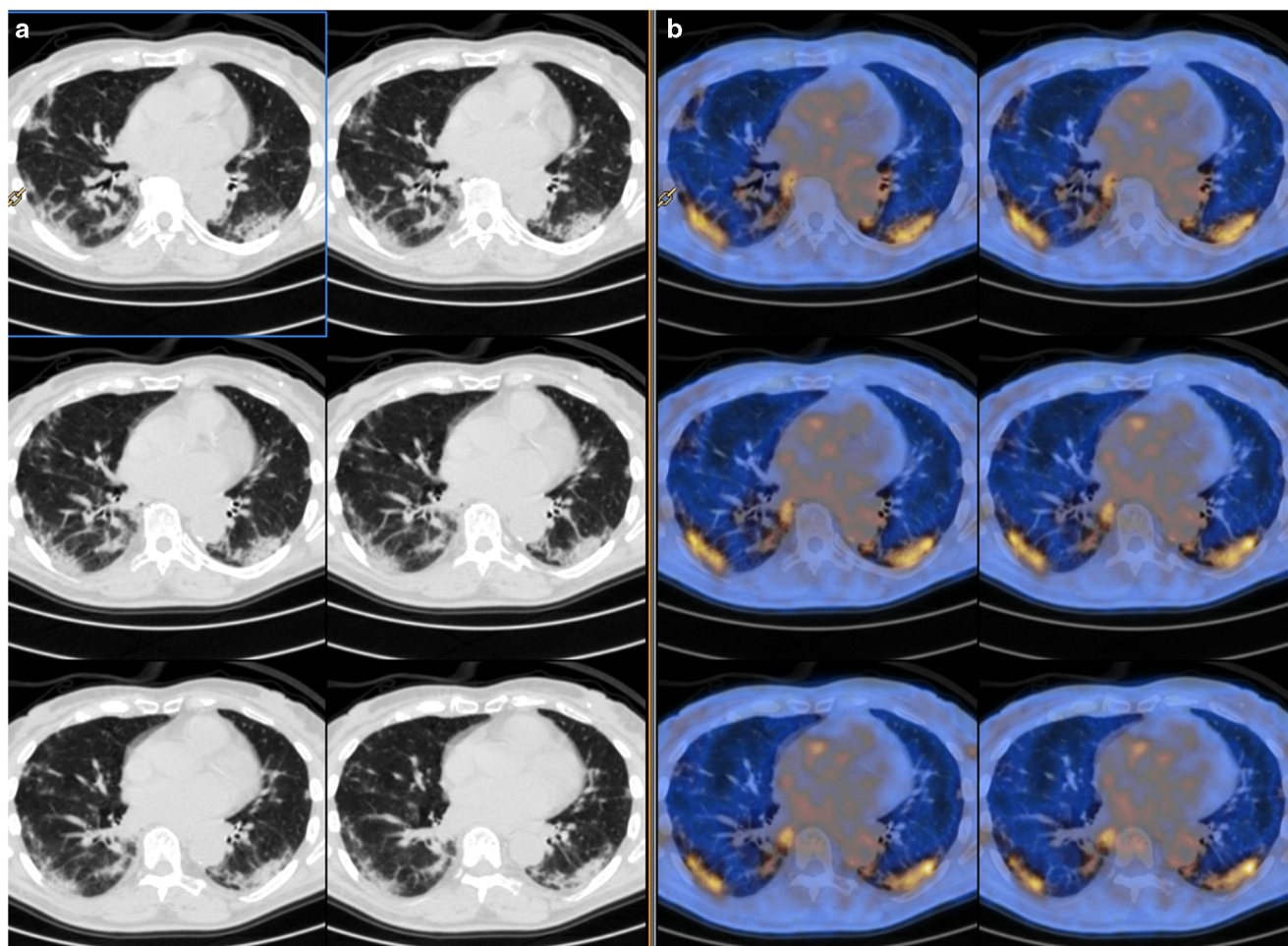


Fig. 5 A 76-year-old patient, affected by breast cancer, who performed the [^{18}F]FDG PET/CT for staging/restaging in COVID-19 period (April). CT (a) (CT axial view) and [^{18}F]FDG PET (b) (fused PET/CT axial view)

were suggestive for interstitial pneumonia. A subsequent PCR test confirmed COVID-19. The images show moderate FDG uptake (SUVmax 2.3) at peripheral ground-glass opacities in lower lung lobes

infection. These results may be related to the low prevalence of COVID-19 in the southern regions of Italy. Consequently, epidemiological data need to be considered at images' evaluation and reporting.

During COVID-19 pandemic, a lower number of patients performed a PET/CT scan: 575 and 723 patients in the COVID-19 period and the COVID-19-free period, respectively. We could speculate that some exams may have been deferred in less sick patients. However, the two cohorts did not statistically differ in terms of age, disease, or scan indication, as shown in Table 1. Consequently, we do not expect our results to be influenced by a patient selection bias.

We included in the study asymptomatic patients with cancer [21] on the occasion of their [^{18}F]FDG PET/CT scans within their standard management. This population is to be considered at high risk of infection because of cancer and

treatment, as well as for their age (mean 65.9 years) [22, 23]. Since this kind of population is potentially more prone to get infected with SARS-CoV-2, it is the most sensitive setting in which an infection spread can be detected. The population of cancer patients undergoing PET/CT is susceptible to get infected by other pathogens causing interstitial pneumonia as well. Therefore, imaging findings are not to be considered pathognomonic of COVID-19, as also supported by our results. Nonetheless, they should guide further testing to identify the pathogen causing interstitial pneumonia, in order to properly treat the patient and safeguard the caregivers, healthcare staff, and the general population.

Additionally, analysis of routinely acquired images may constitute a cost-effective approach. Indeed, several nuclear medicine departments adopted early communication of the lung abnormalities on [^{18}F]-FDG PET/CT to referring

physicians in order to get further testing and confirm or exclude COVID-19 infection [15].

[¹⁸F]-FDG PET/CT cannot be considered a method for COVID-19 screening. Indeed, lung alterations both on CT and PET images are not significantly different among the two cohorts, as illustrated in Fig. 3 and Fig. 4. [¹⁸F]-FDG PET/CT can identify the presence of interstitial pneumonia. Consequently, specific diagnostic tests should be performed. Accordingly, a careful assessment of lung findings should always be included as part of the standard assessment and report, in particular, in case of exceptional circumstance as the COVID-19 pandemic.

Some limitations of our study should be acknowledged. Firstly, the retrospective design which potentially can constitute a bias. Secondly, the diagnosis of COVID-19 was not always possible or available in patients with interstitial pneumonia suspicious for COVID-19 infection on [¹⁸F]-FDG PET/CT. Nonetheless, diagnostic performance was out of the scope of the present investigation. Additionally, RT-PCR on nasopharyngeal swab has been reported to have a suboptimal sensitivity. Finally, we did not exclude patients affected by conditions that could mimic lung abnormalities such as lung cancer, chest radiotherapy, or potentially lung toxic treatments. However, these conditions were taken into account at image assessment.

Conclusion

During COVID-19 pandemic, we detected a statistically significant increase of atypical interstitial lung alterations at routine [¹⁸F]-FDG PET/CT compared with a control COVID-19-free period. The strict overlap, statistically confirmed, of the incidence curves of [¹⁸F]-FDG PET/CT-detected pneumonia and the epidemiological data of the same geographic area support the hypothesis that the increased detection of interstitial pneumonia was partly due to COVID-19. Therefore, testing for SARS-CoV-2 should be performed to assess pneumonia etiology, to limit COVID-19 spread if diagnosis was confirmed. Therefore, nuclear medicine physicians and staff should continue to pay great attention to interstitial pneumonia findings that should drive patients to further diagnostic testing, especially when a new epidemic peak is expected.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent The patients gave their written informed consent to the imaging procedure and the anonymous publication of the images and data for scientific purposes. This study has been notified to the Ethics Committee of Humanitas and Clinical Research Center-IRCCS.

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