



FDG-PET/CT imaging during the Covid-19 emergency: a southern Italian perspective

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Abstract

Purpose To assess the impact of the Covid-19 pandemic on FDG-PET/CT work volume and to evaluate the occurrence of abnormal imaging findings suspicious or potentially diagnostic for interstitial pneumonia by Covid-19 infection in south Italy.

Methods We retrospectively reviewed the number and the findings of FDG-PET/CT studies acquired between February and April 2020 during the Covid-19 pandemic at the University of Napoli Federico II. The number and the findings of FDG-PET/CT studies acquired in the corresponding period of 2019 were also assessed for direct comparison.

Results The number of FDG-PET/CT studies performed during the pandemic ($n = 299$) and in the corresponding period of 2019 ($n = 335$) were comparable. The percentage of abnormal FDG-PET/CT findings, suspicious for interstitial pneumonia by Covid-19 infection, was significantly higher during the pandemic (9%) compared with that found in the corresponding period of 2019 (4%) ($\chi^2 5.45, P = 0.02$). No significant differences were observed in the distribution of Covid-19 reporting and data system (CO-RADS) classification and in the maximum standardized uptake value between the pandemic (2.6 ± 2.2) and the corresponding period of 2019 (3.2 ± 1.4). Of note, patients with abnormal imaging findings during the pandemic time had clinical data and/or laboratory tests negative for Covid-19 infection.

Conclusion Despite the restrictive medical measures for the emergency, the number of FDG-PET/CT studies was unchanged during the pandemic compared with the previous year. Our findings also indicate that Covid-19 infection was contained in our series of patients from southern Italy.

Keywords Covid-19 · SARS-CoV-2 · FDG-PET/CT · Imaging · Southern Italy

Introduction

The recent Covid-19 emergency in Italy determined the reorganization of the healthcare system with subsequent limitations in diagnostic imaging throughput and potential clinical implications for daily medical practice [1–3]. In particular, the policy measures to limit the spread of infection have

determined a decrease in the number of imaging studies requested for clinical indications different from Covid-19 disease. Moreover, hospital adjustments to improve the management of Covid-19 patients are diminishing the volume of conventional medical imaging studies. Of note, outpatient diagnostic imaging may suffer the major impact of these changes, even though the amount of all imaging studies is decreasing. Of course, these changes depend on the site of clinical practice as well as on the evolution of Covid-19 pandemic in different geographic regions. In this emergency context, also ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) imaging studies may be reduced despite the fact that cancer patients require timely FDG scan in different phases of their disease. Furthermore, FDG-PET/CT imaging has been reported to be useful to incidentally diagnose Covid-19 infection as demonstrated by initial experiences in Wuhan as well as in northern Italy [4–8]. The aim of this study was to assess the impact of the Covid-19

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pandemic on FDG-PET/CT work volume and to evaluate the occurrence of abnormal imaging findings suspicious or potentially diagnostic for interstitial pneumonia by Covid-19 infection in southern Italy.

Methods

Patients

We retrospectively reviewed the number and the findings of FDG-PET/CT imaging studies acquired in 2020 between February 3 and April 30, during the Covid-19 pandemic at the University of Napoli Federico II. The number and the findings of FDG-PET/CT imaging studies acquired in the corresponding period of 2019 (February 4 and April 30) were also assessed for direct comparison.

PET/CT imaging

^{18}F -FDG-PET/CT studies were acquired using a Gemini TF 64 scanner (Philips Healthcare, Best, The Netherlands). All patients fasted for at least 6 h prior to imaging, and blood glucose levels were < 180 mg/dL at the time of tracer injection. PET scans were acquired in 3-D mode starting 60 min after ^{18}F -FDG administration (activity range 200–300 MBq, according to body weight). A low- (70 mAs) and high-dose (230 mAs) CT scans (rotation time 1.5 s, collimation 16×0.625) were acquired for attenuation correction of emission data. The sinogram of emission data was reconstructed using the 3-D row action maximum likelihood algorithm, taking into account attenuation, detector efficiency, and scatter and random coincidence corrections. Attenuation correction was performed using CT images. CT and PET images were matched and fused into transaxial, coronal, and sagittal images.

Imaging analysis

CT chest images were evaluated by two experienced radiologists who worked in consensus and reviewed each set in random order to evaluate the presence and the location of abnormal findings in lung parenchyma according to Covid-19 reporting and data system (CO-RADS) classification [9]. In case of disagreement, a third senior radiologist was consulted to reach a final consensus for CT imaging interpretation. Successively, FDG distribution in the lungs was qualitatively evaluated using PET/CT fusion images and maximum standardized uptake value (SUV_{max}) was measured on areas of increased FDG uptake corresponding to abnormal CT findings. SUV_{max} value of the most FDG-avid lung abnormality was recorded. In particular, CO-RADS classification of CT findings [9] represented the level of suspicion of Covid-19

infection graded as not interpretable (CO-RADS 0 = scan technically incomplete or of insufficient quality for artifacts), with no suspicion (CO-RADS 1 = normal CT or non-infectious CT abnormalities), low suspicion (CO-RADS 2 = CT abnormalities consistent with infections other than Covid-19, absence of ground-glass opacities), indeterminate suspicion (CO-RADS 3 = uncertain CT findings for Covid-19 such as small unifocal, perihilar, or homogeneous extensive ground-glass opacities), high suspicion (CO-RADS 4 = unilateral peribronchovascular ground-glass CT opacities without any other typical findings), very high suspicion (CO-RADS 5 = typical bilateral multifocal ground-glass CT opacities with peripheral and/or basal distribution with or without parenchyma consolidations), and as proven very high suspicion (CO-RADS 6 = CO-RADS 5 with positive RT-PCR test for virus-specific nucleic acid).

Statistical analysis

Continuous data are expressed as mean \pm standard deviation and categorical data as percentage. Confidence intervals (CI) were calculated using the Poisson distribution. Student's *t* test and χ^2 test were used to compare the differences in continuous and categorical variables, respectively. Two-tailed *P* values < 0.05 were considered significant. Statistical analysis was performed with Stata 16 software (StataCorp, College Station, Texas, USA). The correlation between CT findings as CO-RADS and tracer activity at FDG-PET was evaluated calculating Spearman's correlation coefficient (ρ).

Results

A total of 299 FDG-PET/CT studies in 288 patients (157 men, mean age 60 ± 17 years) were acquired during the pandemic. The majority (94%) of imaging studies was performed for diagnosis/staging ($n = 102$) or follow-up ($n = 178$) of cancer patients; in particular, 11 patients were studied twice during follow-up. The remaining 19 (6%) imaging studies were acquired for other non-oncological diseases: vasculitis ($n = 4$), endocarditis ($n = 3$), fever of unknown origin ($n = 2$), histiocytosis x ($n = 1$), and other inflammatory diseases ($n = 9$). Similarly, a total of 335 FDG-PET/CT imaging studies in 330 patients (165 men, mean age 61 ± 18 years) were acquired during the corresponding period of 2019. The majority (94%) of imaging studies was performed for diagnosis/staging ($n = 114$) or follow-up ($n = 202$) of cancer patients; in particular, 5 patients were studied twice during follow-up. The remaining 19 (6%) imaging studies were acquired for other non-oncological diseases: fever of unknown origin ($n = 6$), vasculitis ($n = 4$), endocarditis ($n = 2$), histiocytosis x ($n = 1$), mastocytosis ($n = 1$), Chron's disease ($n = 1$), and other inflammatory diseases ($n = 4$). The number of FDG-PET/CT studies performed during

the pandemic ($n = 299$) and in the corresponding period of 2019 ($n = 335$) were comparable ($P = 0.74$).

The percentage of abnormal FDG-PET/CT findings, suspicious for interstitial pneumonia by Covid-19 infection, was significantly higher during the pandemic (9%) compared with that found in the corresponding period of 2019 (4%) ($\chi^2 5.45$, $P = 0.02$).

Abnormal CT findings were observed during the pandemic in 26 patients subjected to the imaging procedure for oncological ($n = 23$) or non-oncological ($n = 3$) diseases. The individual clinical characteristics of these patients are reported in Table 1. In particular, CT abnormalities consisted of CO-RADS 1 ($n = 1$), CO-RADS 2 ($n = 6$), CO-RADS 3 ($n = 15$), CO-RADS 4 ($n = 3$), and CO-RADS 5 ($n = 1$) grading. Of

Table 1 Patient characteristics, CO-RADS classification, and extra-thoracic sites with increased FDG uptake during the pandemic

	Sex	Age (year)	Disease	Phase	Symptoms	Treatment	CO-RADS	Extra-thoracic sites with FDG uptake
1	M	84	Colon cancer	Staging	None	None	2	Liver
2	F	60	Breast cancer	Follow-up	None	Chemotherapy, surgery	3	Local recurrence, axillary LN, thyroid
3	M	75	Lung cancer	Staging	Cough, dyspnea	Immunosuppressive therapy for kidney transplantation	2	None
4	M	64	Rectal cancer	Follow-up	None	Chemotherapy	3	Mediastinal LN
5	M	90	Primary tumor of unknown origin	Diagnosis	Cough, dyspnea, skin rash	None	3	None
6	M	51	Thyroid cancer	Follow-up	None	Targeted therapy	3	Mediastinal LN, liver
7	M	73	Suspected lymphoma	Diagnosis	Fever	None	2	Neck and mediastinal LN, skin, adrenal glands
8	F	77	Non-Hodgkin lymphoma	Follow-up	None	Chemotherapy	3	None
9	F	61	Suspected paraneoplastic syndrome	Diagnosis	Fever, neurological symptoms	None	3	Muscle
10	F	28	Suspected paraneoplastic syndrome	Diagnosis	Neurological symptoms	None	3	Ovary, rectum
11	M	36	Neuroendocrine tumor	Diagnosis	None	None	3	Pancreas, mesenteric and inguinal LN
12	M	80	Laryngeal cancer	Follow-up	Cough, dyspnea	None	5	None
13	F	78	Breast cancer	Follow-up	None	Chemotherapy	3	Adrenal gland
14	F	40	Breast cancer	Follow-up	None	Chemotherapy	3	None
15	F	60	Lung cancer	Follow-up	None	Immunotherapy	2	Neck and axillary LN, parotid
16	M	25	Hodgkin lymphoma	Follow-up	None	Chemotherapy, radiation therapy	4	None
17	M	20	Hodgkin lymphoma	Follow-up	None	Chemotherapy	3	Neck LN, bone
18	M	56	Non-Hodgkin lymphoma	Follow-up	None	Chemotherapy	4	None
19	F	61	Non-Hodgkin lymphoma	Follow-up	Skin rash	Chemotherapy	1	Mediastinal LN
20	F	73	Non-Hodgkin lymphoma	Follow-up	None	Chemotherapy	3	None
21	F	73	Multiple myeloma	Follow-up	Cough, dyspnea	Chemotherapy	2	Neck and mediastinal LN, bone, adrenal glands
22	M	63	Multiple myeloma	Follow-up	None	Chemotherapy	4	Bone
23	F	61	Neuroendocrine tumor	Follow-up	None	None	3	Liver, mesenteric LN
24	M	73	Endocarditis	Diagnosis	Cough, dyspnea	None	3	Mediastinal LN, bone
25	M	92	Fever of unknown origin	Diagnosis	Fever	None	3	Mediastinal LN, colon
26	M	65	Prosthesis infection	Diagnosis	Fever	None	2	Bone

F, female; LN, lymph node uptake; M, male

Table 2 Patient characteristics, CO-RADS classification, and extra-thoracic sites with increased FDG uptake during the corresponding period of 2019

	Sex	Age (year)	Disease	Phase	Symptoms	Treatment	CO-RADS	Extra-thoracic sites with FDG uptake
1	M	72	Oral cavity cancer	Follow-up	None	Chemotherapy, radiation therapy	4	Mediastinal and abdominal LN
2	F	58	Gastric cancer	Staging	None	None	2	Neck, mediastinal, mesenteric and pelvic LN, liver, bone
3	M	78	Suspected lung cancer	Diagnosis	None	None	4	Mediastinal LN, bone
4	M	76	Lung cancer	Staging	Cough, dyspnea	None	3	Bone
5	M	67	Lung cancer	Follow-up	None	Surgery, chemotherapy	3	None
6	M	59	Non-Hodgkin lymphoma	Follow-up	None	Chemotherapy	3	Neck LN
7	M	70	Suspected mediastinal tumor	Diagnosis	None	None	4	None
8	M	15	Sarcoma	Staging	None	None	3	Bone
9	F	41	Thymoma	Staging	Cough, dyspnea, chest pain	None	5	Bone, pituitary gland
10	F	60	Lung cancer	Follow-up	None	Immunotherapy	3	Neck, axillary and mediastinal LN, adrenal gland
11	M	46	Non-Hodgkin lymphoma	Follow-up	None	Chemotherapy	2	Neck LN
12	M	60	Multiple myeloma	Follow-up	Cough, dyspnea	Chemotherapy, bone marrow transplantation	2	Bone
13	M	77	Endocarditis	Diagnosis	None	None	5	Mediastinal LN
14	F	91	Fever of unknown origin	Diagnosis	Cough, dyspnea	None	3	Bone

F, female; LN, lymph node uptake; M, male

note, in all these patients, laboratory tests were negative for Covid-19 infection.

Similarly, abnormal FDG-PET/CT findings were observed during the corresponding period of 2019 in 14 patients subjected to the imaging procedure for oncological ($n = 12$) or non-oncological ($n = 2$) diseases. The individual clinical characteristics of these patients are reported in Table 2. In particular, CT abnormalities consisted of CO-RADS 2 ($n = 3$), CO-RADS 3 ($n = 6$), CO-RADS 4 ($n = 3$), and CO-RADS 5 ($n =$

2). No significant differences were observed in the distribution of CO-RADS findings and in the SUVmax values between the pandemic (2.6 ± 2.2 ; CI 1.7–3.5) and the corresponding period of 2019 (3.2 ± 1.4 ; CI 2.4–4.0) ($P = 0.30$).

Table 3 reports the correlation between CT and FDG-PET findings expressed as CO-RADS and SUVmax in patients with abnormal imaging findings during the pandemic and during the corresponding period of 2019. As shown, no significant correlation was found in both analyzed periods ($\rho = 0.11$ and $\rho = 0.13$). In addition, extra-thoracic sites of increased metabolic activity were observed during the pandemic (Table 1) and the corresponding period of 2019 (Table 2).

Figure 1 shows an example of a patient with laryngeal carcinoma, proven to be Covid-19 infection free, who was studied during the pandemic and presented a CO-RADS 5. Figure 2 shows an example of a thymoma patient studied for staging in 2019 who presented a CO-RADS 5 due to an infection other than Covid-19.

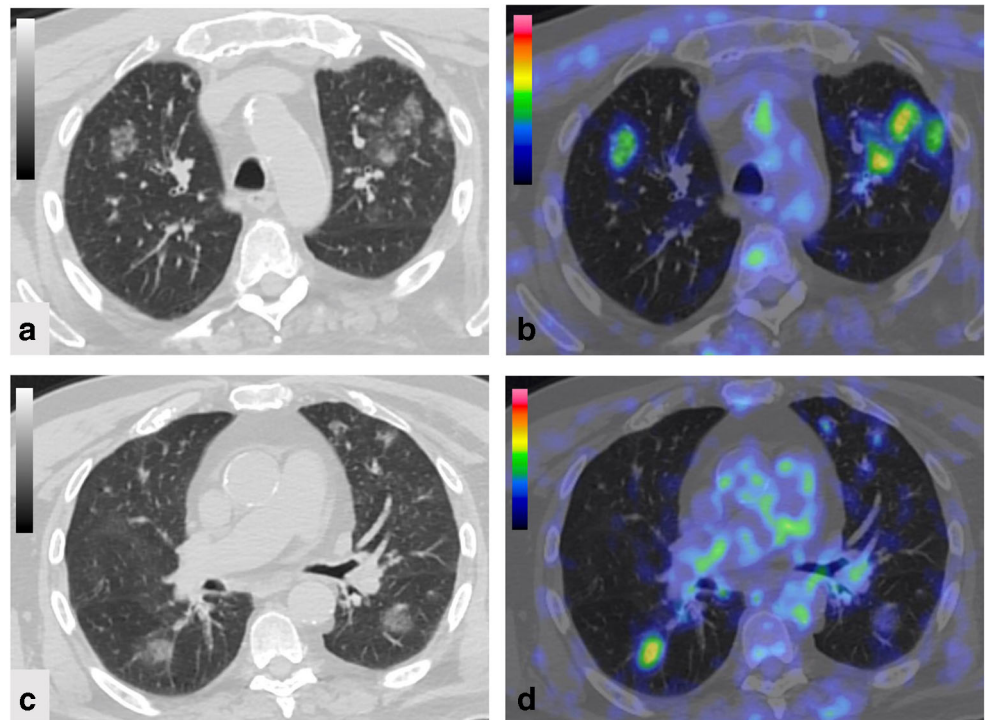
Table 3 Correlation between CT and FDG-PET findings expressed as CO-RADS and SUVmax in patients with abnormal imaging findings during the pandemic and during the corresponding period of 2019

	CO-RADS					ρ
	1	2	3	4	5	
February–April 2020						
Patients (n)	1	6	15	3	1	
SUVmax	2.4	2.5 ± 1.4	1.7 ± 2.2	5.4 ± 3.6	4.0 ± 2.0	0.11
February–April 2019						
Patients (n)	0	3	6	3	2	
SUVmax	-	3.8 ± 1.8	2.4 ± 1.4	3.1 ± 1.0	4.4 ± 1.1	0.13

Discussion

The results of our experience in southern Italy show that, despite the restrictive medical measures for Covid-19

Fig. 1 FDG-PET/CT images in a 80-year-old patient, proven to be Covid-19 infection free, in follow-up for laryngeal carcinoma during the pandemic. CT images (a, c) consisted of CO-RADS 5 finding and FDG-PET/CT images (b, d) showed multiple areas of increased tracer activity with a SUVmax of 6.0

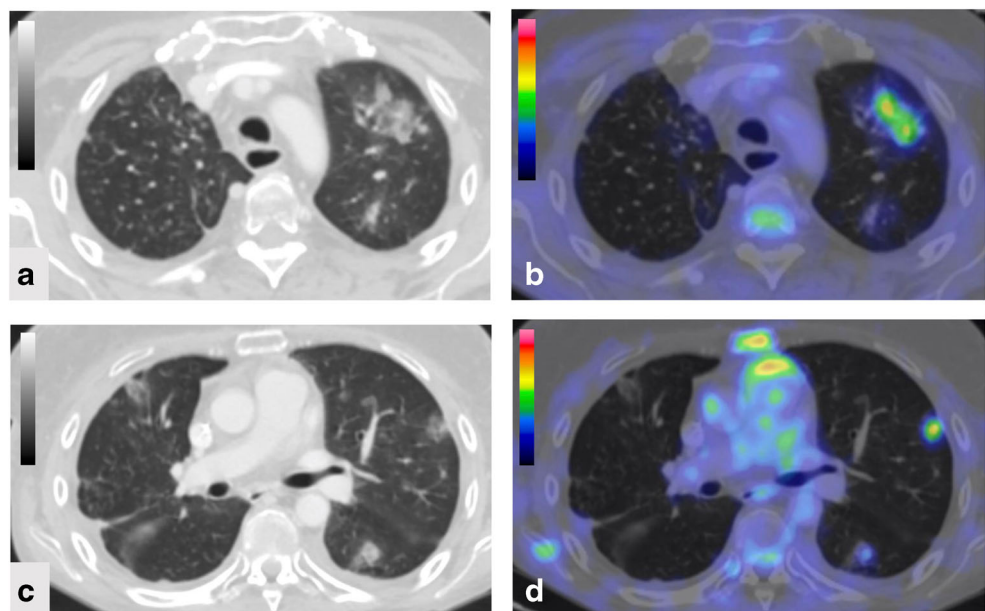


emergency, the number of FDG-PET/CT imaging studies was unchanged during the pandemic compared with the previous year. Yet, the presence of abnormal FDG-PET/CT findings, suspicious for interstitial pneumonia, was not associated with Covid-19 infection, as confirmed by negative clinical data and/or laboratory tests. Of note, on the basis of our findings, CT abnormalities, according to CO-RADS classification, seem to be not specific for Covid-19 infection. Taken together, these preliminary results indicate that Covid-19 infection was contained in our southern Italian patient series.

Conversely, the initial experience in northern Italy [6–8] describing the potential diagnostic usefulness of FDG-PET/CT imaging for Covid-19 infection reported a significant percentage of positive cases reflecting the higher diffusion of the infection in that region.

In our study, the majority (94%) of patients evaluated during the pandemic consisted of patients with oncological diseases in whom imaging studies could not be postponed, thus explaining the unmodified number of FDG-PET/CT studies compared with the corresponding period of 2019. In this

Fig. 2 FDG-PET/CT images in a 41-year-old patient with thymoma studied for staging in 2019 in which CT images (a, c) consisted of CO-RADS 5 finding and FDG-PET/CT images (b, c) showed multiple areas of increased tracer activity with a SUVmax of 3.7



regard, medical measures in Italy were not restrictive for such patients and thus these imaging studies could be performed despite the emergency.

In patients studied during the pandemic, the results of FDG-PET/CT imaging studies did not indicate with certainty the presence of Covid-19 infection in the majority (85%) of cases ($n = 22$). In particular, in such patients, CT findings consisted of CO-RADS 1, 2, or 3, therefore with no suspicion, low, or indeterminate level of suspicion for Covid-19 infection. On the other hand, in the remaining 4 patients (15%), CT findings consisted of CO-RADS 4 ($n = 3$) and CO-RADS 5 ($n = 1$) suggesting a high or very high level of suspicion for Covid-19 infection. However, no cases of Covid-19 infection were proven. Reverse-transcriptase polymerase chain reaction from pharyngeal swabs is considered to be the gold standard for the diagnosis of Covid-19 infection, but a high false-negative rate has been reported [10]. Although CT scan has been showed to be useful in terms of diagnostic sensitivity for Covid-19 infection [11], its accuracy in differentiating such infection from other viral pneumonia was reported to be limited [12]. Our results confirm these observations suggesting a high diagnostic sensitivity, but a low diagnostic specificity.

Similarly, the results of the corresponding period of 2019 showed that the majority (94%) of patients had oncological diseases with no significant difference in terms of initial diagnosis compared with patients enrolled during the pandemic. However, the percentage of abnormal FDG-PET/CT findings (4%) suspicious for interstitial pneumonia corresponding to 2019 period was significantly lower compared with that (9%) of the pandemic. In particular, these findings occurred in 14 patients consisting in the majority (64%) of cases of CT CO-RADS 2 or 3, therefore with low or indeterminate level of suspicion. In the other 36% of cases, CT findings consisted of CO-RADS 4 ($n = 3$) and CO-RADS 5 ($n = 2$) suggesting a high or very high level of suspicion. No cases of Covid-19 infection were proven. Hence, the distribution of CO-RADS findings was similar to that observed during the pandemic time confirming the high sensitivity of CT to detect viral pneumonia other than Covid-19 [11, 12].

FDG-PET/CT imaging has been recently reported to be useful to incidentally diagnose Covid-19 infection as demonstrated by initial experiences in Wuhan and in northern Italy [4–8]. In this regard, Zou et al. [4] initially described a patient of Wuhan with suspected lung malignancy on chest CT who underwent FDG-PET/CT for further evaluation. A large FDG-avid mass was detected in the right lung as well as abnormal tracer uptake was observed in loco-regional lymph nodes as well as in bone marrow. CT fusion images demonstrated the presence of multifocal ground-glass opacities with areas of focal consolidation and laboratory tests confirmed Covid-19 infection. Moreover, Qin et al. [5] described similar findings in additional four patients from Wuhan. Albano et al. [6]

reported their Italian experience in Brescia on incidental FDG-PET/CT findings suggestive of Covid-19 infection in asymptomatic patients living in a high prevalence region of northern Italy. In 6 (9%) of 65 patients with various malignancies, studied in a short period of 10 days, they observed unexpected CT signs of interstitial pneumonia with increased FDG activity due to Covid-19 infection as confirmed by laboratory tests. Similarly, Kirienko et al. [7] and Setti et al. [8] from Bergamo reported a total of six patients with incidental FDG-PET/CT imaging findings suspicious for Covid-19 infection in asymptomatic patients. Therefore, these data show that incidental FDG-PET/CT findings suggestive of Covid-19 infection may occur and hence it is fundamental that nuclear medicine physicians acquire diagnostic skills to recognize typical findings on the co-registered CT images. In this regard, the potential role of FDG-PET/CT in patients with known or suspicious Covid-19 infection has not been demonstrated [13]. An increased FDG uptake in pulmonary or lymph nodal lesions in patients with Covid-19 infection is not surprising as acute inflammatory and infectious pulmonary lesions are characterized by augmented metabolic activity. These findings are not specific for Covid-19 infection and, therefore, FDG-PET/CT should not be recommended for evaluating patients with known or suspected Covid-19 infection. However, these incidental imaging findings should prompt medical staff to adopt all safety measures to protect the population and personnel from exposure to Covid-19 sources [14, 15].

This study has some potential limitations. First, the retrospective design of the study. We did not exclude patients with known lung pathologies that may present with CT features described in Covid-19. It should be also considered that various clinical conditions (e.g., metastasis, therapeutic effects, and therapeutic complications) can determine a radiological simil-Covid-19 pattern. Finally, although patients under medical therapy had a higher CO-RADS value, alternative etiological causes for lung changes could not be clearly determined.

Conclusion

According to our results and other recently reported experiences, FDG-PET/CT imaging may be useful to confirm or ruling out the presence of Covid-19 infection. Nuclear medicine physicians should be on alert since incidental abnormal findings suspicious for Covid-19 may occur on FDG-PET/CT scans. Our preliminary results from an experience in the south of Italy also show that despite the restrictive medical measures for the emergency, the number of FDG-PET/CT studies was unchanged during the pandemic compared with the previous year. Of note, since no cases positive for Covid-19 infection were observed, these imaging data indicate that Covid-19 infection was contained in our series of patients from southern Italy.

Authors' contribution SM, SDV, and AC conceptualized the paper; SM, CGM, CB, AA, and LA evaluated and reported the imaging findings; SM and MP drafted the manuscript; and all the authors revised and commented on the paper and approved the final version of the manuscript.

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 involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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