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Evolution of ^{18}F-FDG-PET/CT Findings in Patients Following COVID-19: An Initial Investigation

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DISCLOSURE

No potential conflicts of interest relevant to this article exist.

Running Title

PET/CT findings following COVID-19

ABSTRACT

Background

The aim of this study was to assess the temporal-evolution of pulmonary ^{18}F-FDG-uptake in patients with Coronavirus Disease (COVID-19) and in Post-COVID-19 Lung-Disease (PCLD).

Methods

Using our hospital's clinical electronic records we retrospectively identified 23 Acute COVID-19, 18 PCLD and 9 completely recovered ^{18}F-FDG-PET/CT studies during the two peaks of UK pandemic. Pulmonary ^{18}F-FDG-uptake was measured as a Target-to-Background Ratio ($TBR_{lung}=SUV_{max}/SUV_{min}$) and compared to temporal stage.

Results

In acute COVID-19, <3 weeks after infection, TBR_{lung} was strongly correlated with time after infection ($r_s=0.81$, $p<0.001$) and was significantly higher in late-stage than early-stage ($p=0.001$). In PCLD TBR_{lung} was lower in patients treated with high-dose steroids ($p=0.003$) and asymptomatic patients ($p<0.001$).

Conclusion

Pulmonary ^{18}F-FDG-uptake in COVID-19 increases with time after infection. In PCLD pulmonary ^{18}F-FDG-uptake rises despite viral clearance suggesting on-going inflammation. There was lower pulmonary ^{18}F-FDG-uptake in PCLD patients treated with steroids.

INTRODUCTION

During February-March 2020, Coronavirus Disease (COVID-19) spread rapidly throughout the UK. COVID-19 may result in viral pneumonitis and Acute Respiratory Distress Syndrome (*1*).

The median time from symptom-onset to intensive-care admission is 10 days, although only 5% of patients are admitted (*1*). This is when anti-viral responses are at a peak, suggesting pneumonitis is a consequence of adaptive immunity (*2*). Persistent respiratory symptoms affect at least one-third of hospitalized patients, some of whom will have Post-COVID-19 Lung-Disease (PCLD) (*3*).

Steroids are critical in reducing mortality from COVID-19 but their role in PCLD is less clear and identifying those that might benefit may be difficult.

Currently, ^{18}F-Fluoro-2-deoxy-D-glucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) has no role in the management of patients with COVID-19 (*4*) and there has been little investigation into the quantification and evolution of ^{18}F-FDG-uptake in COVID-19 (See Supplementary Table 1). Given the growing role of ^{18}F-FDG-PET/CT in Interstitial Lung Diseases (ILD), the primary aim of this preliminary study was to assess the temporal-evolution of ^{18}F-FDG-uptake in COVID-19, and correlate to clinical progression and recovery. A secondary aim was to investigate if steroids could alter this evolution.

MATERIALS AND METHODS

The Institutional Review Board approved this retrospective study and waived the requirement to obtain informed consent. The challenges of the pandemic constrained the methodological design necessitating a retrospective approach.

Patient Selection

All studies performed in the department over the first UK peak of the coronavirus pandemic (March-April 2020) and from September 2020-February 2021 (second-peak) were assessed for acute COVID-19 by following the British Society of Thoracic Imaging guidelines and/or a confirmed history of COVID-19 on the Electronic Health-Record System (EHRS) (*5*). This included some patients without positive Polymerase Chain Reaction (PCR) test results due to the poor availability of PCR tests in the early period. In addition, studies performed for persistent (>4 weeks) respiratory symptoms, in keeping with PCLD, and those who had recovered from COVID-19 after the initial period were also included. Ongoing treatment with steroids and other immunosuppression was recorded. Formal lung function tests were not performed due to infection risks. Acute studies between May and September 2020 were not examined due to the low prevalence and incidence of COVID-19 in London during that time. (See Supplementary Figure 1 and Supplementary Table 2.)

^{18}F-FDG-PET/CT Imaging Protocol

Patients were fasted for at least 6 hours and blood glucose levels were recorded prior to injection of 400MBq ^{18}F-FDG adjusted for weight in keeping with Administration of Radioactive Substances Advisory Committee guidelines (*6*). After an uptake time of 63.1±10.9 minutes whole-body PET scans were acquired in a supine position with the arms above the head with 2-minutes-per-bed position using a General Electric (GE) Discovery-710 PET/CT scanner. A non-enhanced low-dose CT scan was acquired for anatomic co-registration and attenuation correction. Images were reconstructed using a resolution recovery iterative algorithm.

All images were reviewed by at least one dual accredited radiologist nuclear medicine physician. Quantification was performed by investigators with at least 10-years' experience of quantifying PET/CT images in diffuse lung disease. PET analysis was performed blind of clinical history and the CT analysis.

Determination of Temporal Stage

After radiological and EHRS review, the acute COVID-19 cases were assigned to two temporal groups: 'Early' or 'Late', following review of the available clinical history coupled with assessment of the CT components as per well-established findings (*7*): Early COVID-19 (approximately equating to ≤1 week after onset of disease) is defined as predominantly ground-glass opacities with or without associated interlobular thickening this progresses to Late COVID-19 (>1 week after onset of disease to ≤4 weeks), with increasing consolidation and signs of resolution being marked by sub-pleural sparing, development of a fibrous-stripe and crescentic consolidation or reversed halo/atoll sign. Patients who were asymptomatic after 28 days were classed as recovered patients. In addition, patients who were imaged due to persistent symptoms after 28 days were described as having PCLD. The CT component was correlated with other cross-sectional imaging to reduce the likelihood of error of incorrect classification due to breathing artefact. Using this and clinical information from EHRS the number of days since disease onset was estimated.

Quantitative ^{18}F-FDG-PET Analysis

All images were processed using a standard protocol on a dedicated imaging workstation (ADW-volume-4.6 GE-Healthcare) calculated the lung Target-to-Background Ratio ($TBR_{lung}=SUV_{max}/SUV_{mins}$) following the methods described previously (*8–10*).

Statistics

The difference in ^{18}F-FDG-PET uptake measures within the lung against temporal staging and pre-treatment with steroids were assessed using non-parametric Mann-Whitney-test. Results were visualized using Box-and-Whisker plots. All statistical analyses were performed using SPSS-25.0.

RESULTS

Of the 3112 ^{18}F-FDG-PET/CT studies screened 50 met the criteria for study entry, including 18 cases referred for ^{18}F-FDG-PET/CT for investigation of PCLD. Of the 50 cases (median age 61 range 18–87 years), 32 were male (64%), 27 patients were of ethnic minority background (54%): 23 (46%) cases were found to demonstrate acute COVID-19. None of these were intentionally imaged for COVID-19. 9 cases demonstrated asymptomatic recovered COVID-19 confirmed on the EHRS. (See Supplementary Tables 3-5.)

In the other 18 of the 50 cases imaging was performed because of persistent shortness of breath and respiratory symptoms in keeping with PCLD – all 18 had been admitted to hospital requiring oxygen. 15 of these patients previously had positive PCR tests and COVID-19 was clinically diagnosed in the others. 9 had ongoing treatment with steroids for PCLD, the other 9 were not receiving treatment for their PCLD. All PCLD patients had been re-swabbed prior to PET imaging and confirmed as PCR negative. (See Supplementary Table 5.)

Temporal Stage

Following review of the attached CT component (lung windows) and available clinical history, of the 23 acute COVID-19 patients: 8 (35%) were determined to represent early COVID-19 and 15 (65%) late. (See Figure 1 and Supplementary Table 5.)

Association of Pulmonary ^{18}F-FDG-Uptake with Temporal-staging in Early & Late Stage Disease

^{18}F-FDG-uptake analysis of the lung lesions in the acute patients demonstrated increasing TBR_{lung} over time with the progression from low avidity ground-glass change to avid consolidation during the late phase (Median Early-stage: SUV_{max} 1.6, TBR_{lung} 6.4; Late-stage: SUV_{max} 4.0, TBR_{lung} 13.7). In the acute patients, TBR_{lung} was significantly different for late-stage patients having a higher TBR_{lung} than early stage patients (p=0.001, See Figure 2.). Amongst these patients, a significant positive correlation was observed between TBR_{lung} and estimated time since onset,

(r_s=0.60, p=0.003, See Figure 3.), this was stronger when limited to acute patients estimated to be in the first 3 weeks of infection (n=18, r_s=0.81, p<0.001).

Pulmonary ^{18}F-FDG-Uptake in PCLD

There was lower TBR_{lung} in patients who had received treatment with high-dose steroids (p=0.003) (See Figure 2.) (Median steroid-treated: SUV_{max} 2.4, TBR_{lung} 6.62; untreated: SUV_{max} 5.8, TBR_{lung} 18.1)

TBR_{lung} was lower in asymptomatically recovered patients (Median SUV_{max} 1.2, TBR_{lung} 4.6) than both untreated PCLD patients and those treated with steroids. (p<0.001 and p=0.020 respectively, Kruskal-Wallis for all 3 groups p<0.001).

DISCUSSION

This study is the first attempt to characterise the evolution of pulmonary ^{18}F-FDG-uptake in patients with COVID-19 assigned a temporal stage (Early-to-Late-to-PCLD) based on clinical context and CT findings.

The increase of lung avidity with time suggests increasing lung inflammation (*11*,*12*) in acute COVID-19. In most cases, ^{18}F-FDG-uptake would then be expected to decrease with viral clearance and establishment of immunity. There is, however, a subset of COVID-19 patients with delayed recovery that continue to show significant ^{18}F-FDG-uptake, reminiscent of our findings in ILD (*8*,*9*,*13*,*14*), and raising the possibility that COVID-19 pneumonitis is associated with an activated host immune response rather than direct viral pathology (*12*,*15*,*16*). It would be useful to understand the ability of lung avidity to predict clinical course or the likelihood of development of a post-COVID-19 ILD, in this patient-cohort.

The RECOVERY study, which this study pre-dates, demonstrated survival benefit with steroids in hypoxic patients with COVID-19 (*15*). In our study, several patients went on to develop an inflammatory organising-pneumonia, characterised by persistent and increasing ^{18}F-FDG-uptake. Steroid therapy is a recognised treatment for organizing-pneumonia and other inflammatory ILDs (*15*), and in those cases treated with post-discharge steroids, ^{18}F-FDG-uptake was consistently lower. Our findings raise the question of whether steroid administration has a role, not just for acute hypoxia but also in the later stages of COVID-19 and for PCLD. This approach has been debated (*15*) with calls for a randomized-control trial to define the role of steroid therapy more widely. Although imaging may be useful, it is hard to determine from CT whether parenchymal changes indicate reversible inflammation or irreversible fibrosis. It is possible that ^{18}F-FDG-PET/CT may offer a sensitive and specific biomarker to guide and rationalise steroid treatment.

Limitations

Given the challenges of nuclear medicine imaging in the pandemic this study has methodological limitations. They are directly related to the infectious and emergent epidemic, the workload and severe capacity restraints of PET/CT departments, staff protection and equipment sterilization, and the medical instability of seriously ill COVID-19 patients. This limits patient numbers, preventing the use of a control group and longitudinal ^{18}F-FDG-PET/CT imaging. Diagnostic CT will likely remain the most practical way to investigate acute COVID-19, although PET imaging may give potential mechanistic insights. However, PCLD patients are not currently believed to be an infection risk and thus performing longitudinal ^{18}F-FDG-PET/CT studies in this population may be realistic and feasible. This study was not prospectively designed to study the use of steroid in PCLD however statistically-significant lower ^{18}F-FDG-uptake in PCLD patients with steroid administration versus those without was observed. Finally, the lack of PCR testing in the first wave, as well as the high incidence of asymptomatic cases throughout the pandemic, creates uncertainties in prevalence and thus retrospective analysis may suffer from selection bias. Despite design limitations, the findings of this study offer some insight into the development of pulmonary disease in COVID-19 and can help provide the evidence to justify performing formal prospective studies on this topic in future.

CONCLUSION

^{18}F-FDG-uptake in COVID-19 increases with time after infection and correlates with severity. Persistent ^{18}F-FDG-uptake is seen in patients with PCLD disease. These findings suggest that future studies may be directed at the use of ^{18}F-FDG-PET/CT to understand disease trajectory and may aid management of those patients with persistent respiratory symptoms

ACKNOWLEDGMENTS

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KEY POINTS

Question:

What is the temporal-evolution of ^{8}F-FDG-uptake in COVID-19 and in PCLD?

Pertinent Findings:

^{18}F-FDG-uptake is shown to increase with time after COVID-19 infection. Steroid treatment is associated with reduced uptake in PCLD.

Implications for Patient Care:

^{18}F-FDG-PET/CT may help understand disease trajectory and aid management of PCLD.

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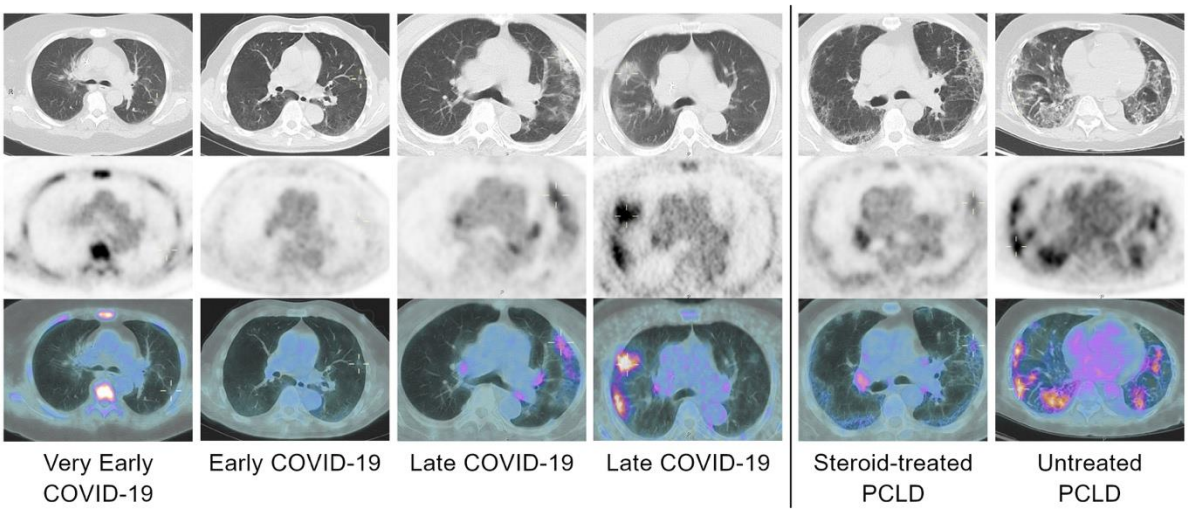
1

Graphical Abstract:



FIGURES

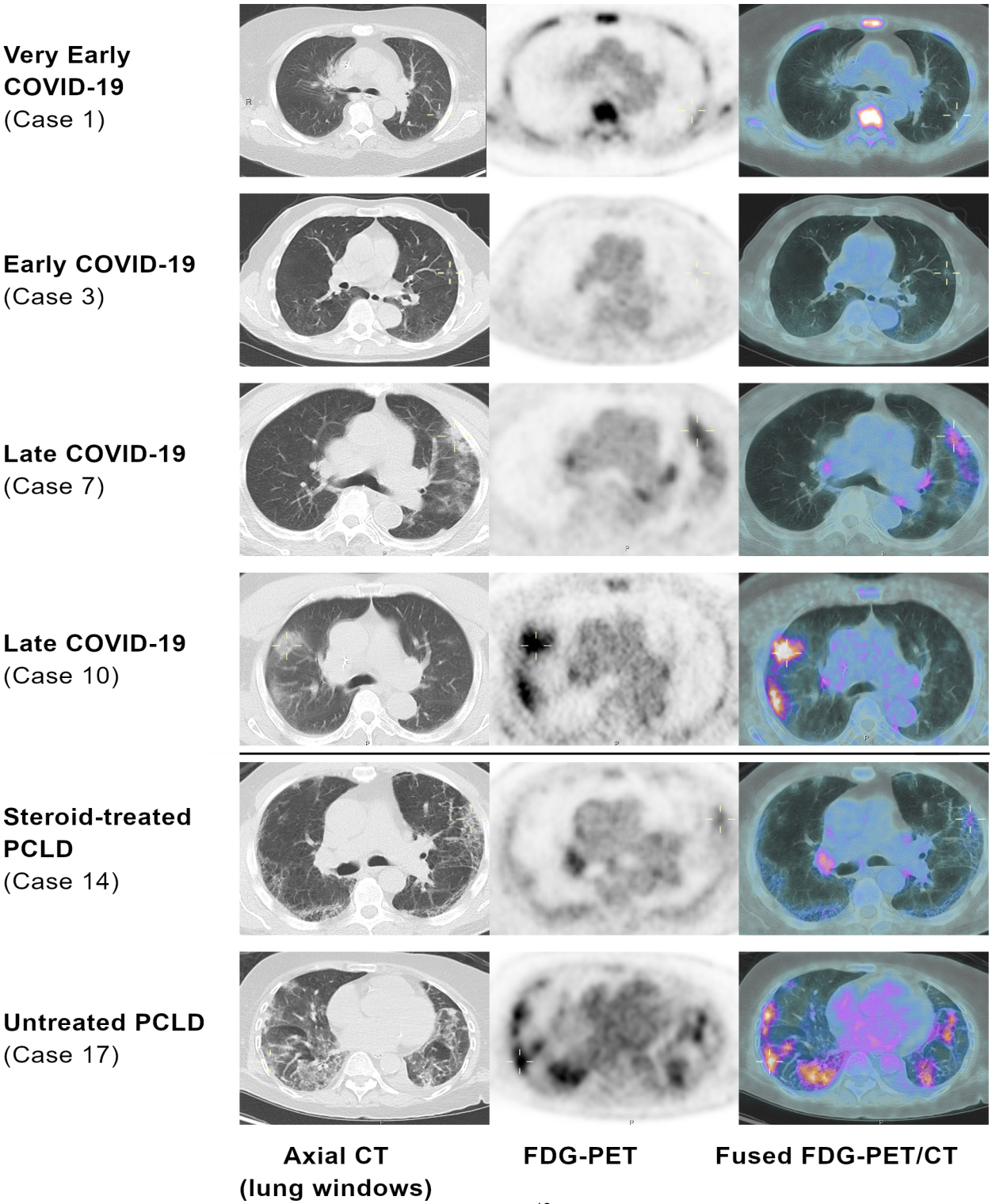


FIGURE 1 Exemplar images demonstrating increasing ^{18}F-FDG-uptake with temporal stage and lower ^{18}F-FDG-uptake in steroid-treated PCLD. (Lung-windowed Axial-CT, ^{18}F-FDG-PET windowed SUV 0–5 and fused ^{18}F-FDG-PET/CT images.)

Medullary uptake in case 1 was due to leukaemia and not COVID-19.

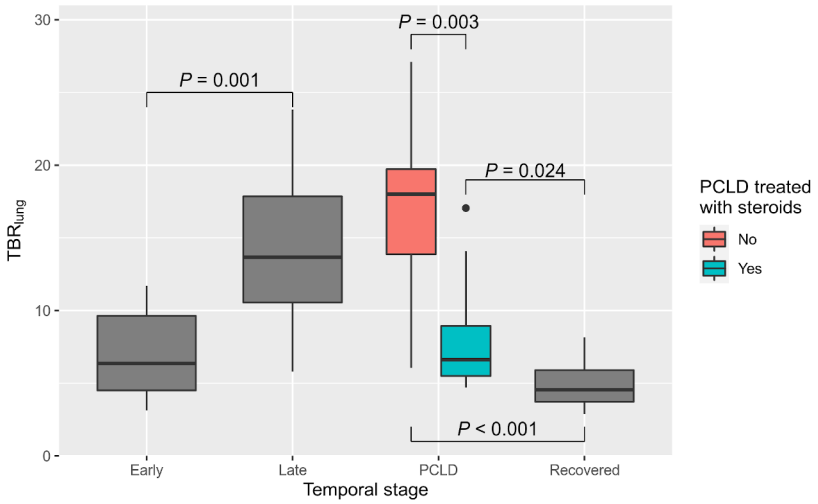


FIGURE 2 ^{18}F-FDG-uptake (TBR_{lung}) by temporal stage

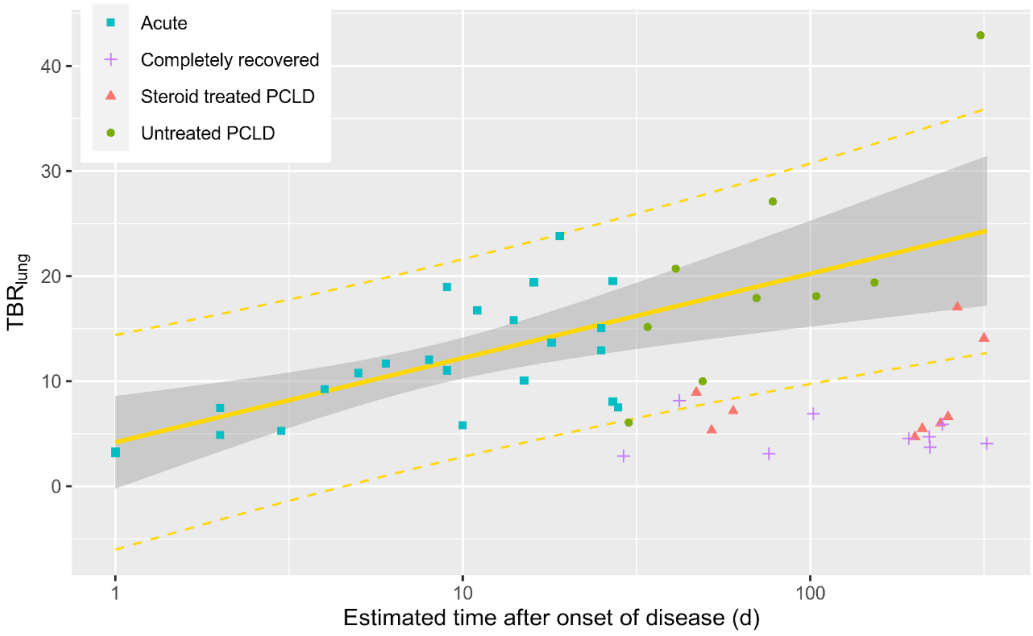


FIGURE 3 ^{18}F-FDG-uptake (TBR_{lung}) against the Estimated time after onset of disease (on a logarithmic scale) with superimposed regression using the 23 acute (early & late) patients. (F-statistic=14.94, p<0.001. Spearman's r_s=0.595, p=0.003.) **Steroid treatment means ≥10 days high-dose steroid treatment.**

Supplementary Material

FIGURES

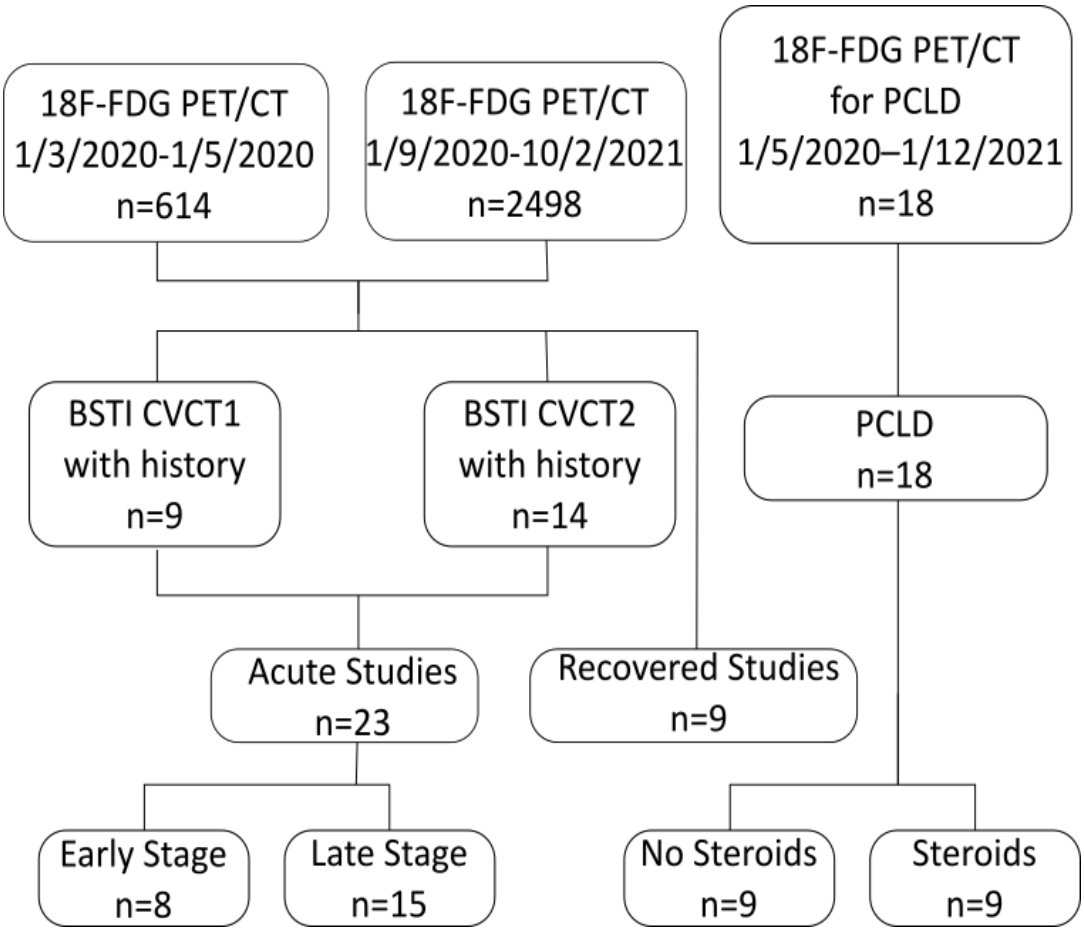


FIGURE 1 STARD flow chart of study selection.

TABLES

Previous Study Type	Number of papers
Individual case reports demonstrating ^{18}F-FDG avidity	23
Case series: • 1 paper with 5 patients • 1 paper with 5 patients • 1 paper with 4 patients • 1 paper with 5 patients • 1 paper with 6 patients • 1 paper with 4 patients	6
Incidence & Prevalence of COVID-19 in PET/CT	3
Discussion of the potential future role of PET/CT	3

TABLE 1 Results of literature review of published papers on COVID-19 and ^{18}F-FDG PET/CT

Inclusion Criteria
^{18}F-FDG-PET/CT performed within period of acute study collection or referred for PCLD study
BSTI CVCT1 or CVCT2 changes on CT component of scan **or** CVCT0 and previous confirmed history of COVID-19 compatible with asymptomatic recovery.
Clinical history compatible with COVID-19 available on electronic health records
Exclusion Criteria
BSTI CVCT0, CVCT3 changes on CT component **except** when previously confirmed COVID-19 disease and considered recovered
No clinical history available or CVCT2 changes explained by other pathology

TABLE 2 Inclusion and Exclusion criteria

Indications	Number of patients
Non-thoracic Cancer	19
Pyrexia of Unknown Origin	2
Paraneoplastic Syndrome	1
Vasculitis	1

TABLE 3 Indications of the acute cases

Indications	Number of patients
Non-thoracic Cancer	6
Musculoskeletal Inflammation	1
Paraneoplastic Syndrome	1
Cardiac Sarcoid	1

TABLE 4 Indications of the asymptomatic recovered cases

Case Number	Age at scan (years) & Sex	Temporal Stage	Estimated Time since onset of disease (days)	Admitted to Hospital	PCR Proven	CRP (mg/L)	ESR (mm/hr)	D-Dimer (µg/L FEU)	SpO_2 during scan	Oxygen during scan	Inpatient at time of scan	Steroid Therapy
1	61F	Early	Early (1–3)	y	y	9.6	—	810	95%	RA	y	n
2	58F	Early	Early (3–7)	n	—[a]	—	—	—	—	RA	n	n
3	72M	Early	Early (3–7)	n	—[a]	—	—	—	—	RA	n	n
4	43F	Early	Early (3–7)	n	—[a]	—	—	—	—	RA	n	n
5	68F	Early	Borderline Early (4–9)	y	y	—	—	—	95%	2L NC	y	n
6	62M	Late	Borderline Late (7–10)	y	y	37.5	—	—	96%	RA	y	n
7	84M	Late	Late (9–14)	n	—[a]	—	—	—	—	RA	n	n
8	18F	Late	Late (10–14)	y	n	228.7	8	2478	97%	RA	y	n
9	76M	Late	Late (11–14)	y	y	6.8	—	1970	98%	RA	y	n
10	60M	Late	Late (11–14)	n	—[a]	—	—	—	—	RA	n	n
11	64M	Late	Late (11–14)	n	—[a]	—	—	—	97%	RA	n	n
12	60M	PCLD	28–36	y	n	1.0[c]	—	—	100%	RA	y	n
13	80M	PCLD	30–38	y	y	—[c]	—	—	92%	1L NC	y	n
14	60M	PCLD	42–52	y	n	8.4[c]	—	—	97%	RA	y	y
15	71M	PCLD	48–56	y	y	—[c]	—	—	94%[b]	RA	n	y
16	68F	PCLD	54–64	y	n	14.7[c]	—	—	95%	1L NC	y	y
17	72F	PCLD	64–74	y	y	121.6[c]	—	—	91%	RA	y	n
18	60F	PCLD	70-85	y	y	—[c]	—	—	96%[b]	RA	n	n
19	60M	PCLD	150–160	y	y	121.2[c]	70	300	96%	RA	n	n
20	56M	PCLD	210–215	y	y	1.2[c]	—	—	95%	RA	n	y
21	27F	Recovered	76–80	y	y	—	—	—	100%	RA	n	n
22	39M	Recovered	26–30	y	y	—	—	—	99%	RA	n	n
23	58M	PCLD	195–205	y	y	63.7[c]	120	1080	95%	RA	n	y
24	60M	PCLD	260–270	y	y	51.9[c]	28	190	99%	RA	n	y
25	51M	Recovered	180–200	y	y	—	—	—	95%	RA	n	n
26	45M	PCLD	100–120	n	y	14.5[c]	—	500	95%	RA	n	n
27	61M	PCLD	240–250	y	y	0[c]	—	1280	95%	RA	n	y
28	72M	PCLD	45–52	y	y	122.8[c]	111	1570	99%	RA	y	n
29	47F	Late	Borderline Late (9–12)	y	y	43.4	—	390	99%	RA	y	n
30	61M	PCLD	232–242	y	n	11.9[c]	—	—	100%	RA	n	y
31	48M	Late	Late (20–30)	y	y	5.7	5	1690	99%	RA	y	n
32	70M	PCLD	39–43	y	y	—	—	—	95%	RA	y	n
33	87F	Late	Late (22–28)	y	y	38.7	—	1290	92%	1L NC	y	n
34	66M	PCLD	309–320	y	y	—	—	—	95%	2L NC	n	y
35	59F	Late	Late (13–18)	n	y	—	—	—	97%	RA	n	n
36	51F	Late	Late (15–25)	n	y	—	—	—	95%	RA	n	n
37	87F	Early	Early (5–7)	y	y	10.4	27	—	96%	RA	y	n
38	61M	Recovered	215–225	n	y	—	—	—	97%	RA	n	n
39	79M	Recovered	200–240	n	y	—	—	—	95%	RA	n	n
40	60F	Early	Early (1–3)	n	y	—	—	—	95%	RA	n	n
41	51M	Late	Late (26–28)	y	y	—	—	1380	95%	RA	n	n
42	60M	Recovered	200–220	n	—[a]	—	—	—	96%	RA	n	n
43	61M	Late	Late (20–28)	y	n	—	—	—	95%	RA	n	n
44	61F	PCLD	300–315	y	y	—	—	—	96%	RA	n	n
45	79M	Late	Late (19–23)	y	y	—	—	—	98%	RA	y	n
46	61M	Recovered	317–330	y	y	—	—	—	95%	RA	n	n
47	61M	Recovered	38–44	y	y	—	—	—	97%	RA	n	n
48	75F	Late	Late (25–28)	y	y	—	—	—	94%	2L NC	y	n
49	74F	Recovered	90–120	n	y	—	—	—	95%	RA	n	n

50	80M	Early	Early (1–3)	y	y	—	—	—	96%	RA	y	n

TABLE 5 Distribution and Clinical Parameters

[a] At the time of infection availability of PCR testing was limited to only patients admitted to hospital

[b] Saturations measured on different day to imaging. RA: Room Air; NC: nasal cannulae

[c] CRP was noted to be falling from peak for all Delayed Recovery patients

—: Test not performed

Steroid therapy was defined as high dose steroids for 10 days or more

Please note: formal lung function tests were not performed on these patients due to the pandemic.