FULL PAPER

A case–control evaluation of pulmonary and extrapulmonary findings of incidental asymptomatic COVID-19 infection on FDG PET-CT

1,2MANIL SUBESINGHE, MBBS, MRCP, FRCR, 1,2SHAHEEL BHUVA, 1,2JOEL T DUNN, 1,2ALEXANDER HAMMERS, 1,2GARY J COOK, 1,2SALLY F BARRINGTON and 1,2BARBARA M FISCHER

1King’s College London & Guy’s and St. Thomas’ PET Centre, London, UK
2Department of Cancer Imaging, School of Biomedical Engineering and Imaging Sciences, King’s College London, London, UK

Address correspondence to: Dr Manil Subesinghe
E-mail: manil.subesinghe@kcl.ac.uk

Objectives: To describe the findings of incidental asymptomatic COVID-19 infection on FDG PET-CT using a case–control design.

Methods: Incidental pulmonary findings suspicious of asymptomatic COVID-19 infection on FDG PET-CT were classified as a confirmed (positive RT-PCR test) or suspected case (no/negative RT-PCR test). Control cases were identified using a 4:1 control:case ratio. Pulmonary findings were re-categorised by two reporters using the BSTI classification. SUV metrics in ground glass opacification (GGO)/consolidation (where present), background lung, intrathoracic nodes, liver, spleen and bone marrow were measured.

Results: 7/9 confirmed and 11/15 suspected cases (COVID-19 group) were re-categorised as BSTI 1 (classic/probable COVID-19) or BSTI 2 (indeterminate COVID-19); 0/96 control cases were categorised as BSTI 1. Agreement between two reporters using the BSTI classification was almost perfect (weighted χ² = 0.94). SUVmax GGO/consolidation (5.1 vs 2.2; p < 0.0001) and target-to-background ratio, normalised to liver SUVmean (2.4 vs 1.0; p < 0.0001) were higher in the BSTI 1 & 2 group vs BSTI 3 (non-COVID-19) cases. SUVmax GGO/consolidation discriminated between the BSTI 1 & 2 group vs BSTI 3 (non-COVID-19) cases with high accuracy (AUC = 0.93). SUV metrics were higher (p < 0.05) in the COVID-19 group vs control cases in the lungs, intrathoracic nodes and spleen.

Conclusion: Asymptomatic COVID-19 infection on FDG PET-CT is characterised by bilateral areas of FDG avid (intensity > x2 liver SUVmean) GGO/consolidation and can be identified with high interobserver agreement using the BSTI classification. There is generalised background inflammation within the lungs, intrathoracic nodes and spleen.

Advances in knowledge: Incidental asymptomatic COVID-19 infection on FDG PET-CT, characterised by bilateral areas of ground glass opacification and consolidation, can be identified with high reproducibility using the BSTI classification. The intensity of associated FDG uptake (>x2 liver SUVmean) provides high discriminative ability in differentiating such cases from pulmonary findings in a non-COVID-19 pattern. Asymptomatic COVID-19 infection causes a generalised background inflammation within the mid-lower zones of the lungs, hilar and central mediastinal nodal stations, and spleen on FDG PET-CT.

INTRODUCTION
The coronavirus disease 2019 (COVID-19) pandemic has created the biggest global health crisis in generations. The spread of infection has been difficult to control due to asymptomatic infection, estimated to account for over 50% of all transmissions. Nasopharyngeal swab reverse transcriptase polymerase chain reaction (RT-PCR) is considered the gold standard for diagnosing COVID-19 infection. The sensitivity of RT-PCR in symptomatic patients ranges between 82 and 97% but detection rates are lower in asymptomatic individuals.

During the early stages of the pandemic in 2020, numerous studies described computed tomography (CT) features characteristic of COVID-19 infection with some suggesting sufficient diagnostic accuracy of CT in the absence of RT-PCR testing; significant selection bias and several confounding factors have since undermined such conclusions. International guidelines and a recent umbrella review recommend CT as a problem-solving tool to identify complications of COVID-19 infection or when an alternative diagnosis is suspected in asymptomatic individuals.
Table 1. Details of confirmed and suspected cases of COVID-19 infection

| Case | Age (years) | Gender | Scan indication         | SUV\textsubscript{max} GGO/consolidation | BSTI classification | RT-PCR status (days after FDG PET-CT) | COVID-19 status | 6-month imaging follow-up |
|------|-------------|--------|-------------------------|------------------------------------------|--------------------|---------------------------------------|----------------|----------------------------|
| 1    | 59          | Male   | Head & Neck cancer      | 7.2                                      | 1                  | Negative (1 day)                      | Suspected       | Resolution on 4 month f/u PET-CT. |
| 2    | 65          | Female | Melanoma                | 3.6                                      | 3                  | None                                  | Suspected       | Resolution on 2 month f/u CT thorax. |
| 3    | 42          | Female | Lymphoma                | 7.0                                      | 3                  | Positive (0 days)                      | Confirmed       | Pulmonary fibrosis on 6 month f/u CT thorax. |
| 4    | 72          | Female | Head & Neck cancer      | 6.1                                      | 2                  | None                                  | Suspected       | Resolution on 2 month f/u CT thorax. |
| 5    | 52          | Male   | Oesophageal cancer      | 8.7                                      | 1                  | Positive (22 days)                     | Confirmed       | Resolution on 3 month f/u PET-CT. |
| 6    | 86          | Male   | Melanoma                | 5.6                                      | 2                  | None                                  | Suspected       | No further imaging.            |
| 7    | 76          | Male   | Cardiac infection       | 4.1                                      | 1                  | Positive (3 days)                      | Confirmed       | No further imaging.            |
| 8    | 63          | Female | Myeloma                 | 3.2                                      | 2                  | None                                  | Suspected       | Resolution on 5 month f/u chest radiograph. |
| 9    | 66          | Male   | Lymphoma                | 6.7                                      | 1                  | None                                  | Suspected       | Resolution on 4 month f/u CT thorax. |
| 10   | 51          | Male   | Lymphoma                | 3.5                                      | 3                  | None                                  | Suspected       | No further imaging.            |
| 11   | 69          | Male   | Melanoma                | 3.9                                      | 1                  | None                                  | Suspected       | Resolution on 3 month f/u PET-CT. |
| 12   | 54          | Male   | Pancreatic cancer       | 7.8                                      | 1                  | Positive (7 days)                      | Confirmed       | Resolution on 4 month f/u CT thorax. |
| 13   | 49          | Female | Lymphoma                | 3.8                                      | 2                  | None                                  | Suspected       | Resolution on 1 month f/u PET-CT. |
| 14   | 66          | Female | Endometrial cancer      | 2.0                                      | 1                  | Negative (1 day)                       | Suspected       | Resolution on 2 month f/u PET-CT. |
| 15   | 64          | Female | Lung cancer             | 2.1                                      | 1                  | None                                  | Suspected       | Resolution on 2 month f/u PET-CT. |
| 16   | 51          | Female | Lymphoma                | 0.7                                      | 3                  | None                                  | Suspected       | No further imaging.            |
| 17   | 49          | Female | Oesophageal cancer      | 2.3                                      | 3                  | None                                  | Suspected       | No further imaging.            |
| 18   | 39          | Female | Unknown malignancy      | 4.0                                      | 2                  | Negative (1 day)                       | Suspected       | No further imaging.            |

(Continued)
criteria for the diagnosis of COVID-19 infection on CT, based on the presence and distribution of ground glass opacification (GGO), consolidation and varied patterns of organising pneumonia (OP). Asymptomatic individuals can have normal lungs on CT or alternatively demonstrate radiological features compatible with COVID-19 infection. Several case reports/series of asymptomatic COVID-19 infection on 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography (PET)-CT report metabolically active findings mainly confined to the lungs and mediastinal lymph nodes; most studies have been purely descriptive, however. A few studies reporting increased FDG uptake in extrathoracic nodes, spleen, and bone marrow, suggest that FDG PET-CT can demonstrate the immune response to viral infections. Identifying incidental COVID-19 infection can alter patients’ immediate management and reduce the risk of transmission to others and is of particular importance to cancer patients who are at increased risk from COVID-19 infection.

**OBJECTIVE**

Our hypothesis is that asymptomatic COVID-19 infection on FDG PET-CT imaging manifests as areas of FDG avid GGO/consolidation on the background of generalised inflammation in the lungs and other extrapulmonary locations. We will assess whether pulmonary and extrapulmonary findings on FDG...
Incidental asymptomatic COVID-19 infection on FDG PET-CT

PET-CT in patients with suspected asymptomatic COVID-19 infection scanned during the ‘first wave’ of UK pandemic, are significantly different to those in a control group scanned prior to the pandemic, matched for age, gender and scan indication. We will also determine the ability of FDG uptake in conjunction with pulmonary findings categorised using the BSTI classification to discriminate between COVID-19 and non-COVID-19 infection, whilst assessing the interobserver agreement between two reporters using the BSTI classification.

METHODS

Case selection

Institutional review board approval was obtained for this retrospective non-interventional observational case–control study. Inclusion criteria were:

- FDG PET-CT examination performed between 23/03/2020 and 29/05/2020 during the ‘first wave’ of the UK pandemic.
- Absence of new continuous cough or high temperature, i.e., asymptomatic.

PET-CT in patients with suspected asymptomatic COVID-19 infection scanned during the ‘first wave’ of UK pandemic, are significantly different to those in a control group scanned prior to the pandemic, matched for age, gender and scan indication. We will also determine the ability of FDG uptake in conjunction with pulmonary findings categorised using the BSTI classification to discriminate between COVID-19 and non-COVID-19 infection, whilst assessing the interobserver agreement between two reporters using the BSTI classification.
• Expedited (via email notification) FDG PET-CT report due to incidental pulmonary findings suspicious for asymptomatic COVID-19 infection.

Referring clinicians either opted for confirmation of COVID-19 infection via RT-PCR hospital testing or recommendation for a period of self-isolation for 14 days as per UK government guidance due to a lack of community testing at the time. 30 Patients with a positive RT-PCR test within 28 days of scanning were classified as a confirmed case. Patients with pulmonary findings suspicious of COVID-19 infection on FDG PET-CT but no or negative RT-PCR test within 28 days of scanning were classified as a suspected case. Information on RT-PCR testing and clinical follow-up was obtained from institutional electronic databases.

Consecutive control cases matched for age, gender and scan indication without exclusion criteria were identified from spring 2019 ± 3 months, using a 4:1 control: case ratio.

FDG PET-CT imaging review

FDG PET-CT examinations were performed using methodology aligned to EANM guidance and described previously. 31 All examinations were anonymised (including date of examination) and analysed using Hybrid Viewer (Hermes Medical Solutions, Sweden). Independent blinded review of pulmonary findings was undertaken 6 months after the ‘first wave’ by board certified radiologists (S.B) and consultant radiologist (M.S) with 1 and 10 years of PET-CT reporting experience, respectively, and each with 12 years of diagnostic CT (including thoracic CT) reporting experience. Pulmonary findings were categorised using the BSTI classification 12; classic/probable COVID-19 (BSTI 1), indeterminate COVID-19 (BSTI 2), non-COVID-19 (BSTI 3), and normal (BSTI 4). The normal category (BSTI 4) included findings considered within the spectrum of normality for PET-CT, e.g., gravity-dependent GGO and basal linear atelectasis. Following independent review, examinations with disagreement in BSTI classification had consensus reads. For examinations with clinically significant pulmonary parenchymal findings, i.e., BSTI 1–3, the highest maximum standardised uptake value (SUV max) in an area of GGO/consolidation was documented, enabling target-to-background ratio (TBR) calculation, normalised to the mean standardised uptake value (SUV mean) in the liver.

SUV metrics were derived from normal lung and from extrapulmonary sites (intrathoracic nodes, liver, spleen and bone marrow) by a consultant nuclear medicine physician (B.M.F) with 15 years of PET-CT reporting experience. Freehand regions of interest (ROIs) following the contours of the lungs but excluding subpleural regions and avoiding major vessels or parenchymal abnormalities were drawn in the upper (level of suprasternal notch), mid (1 cm below the carina) and lower zones (2.5 cm above the right hepatic dome) of both lungs to calculate SUV mean of background lung. ROIs were drawn around the major intrathoracic nodal stations 32 to calculate nodal SUV max; SUV max was only measured if lymph nodes were visible on CT. Spherical volumes of interest (VOIs) were placed in the right lobe of the liver (6 cm diameter), spleen (3 cm diameter) and L4 vertebral body (2 cm diameter) as a representation of marrow uptake, to calculate SUV mean in these VOIs.

Statistical analysis

Interobserver agreement using the BSTI classification was assessed using the weighted κ method. 33 Non-parametric tests were used to assess for group-wise (Kruskal-Wallis) and pairwise (Mann Whitney U) differences. The Benjamini-Hochberg method to estimate the false discovery rate (FDR) was used to correct for multiple comparisons; an FDR < 0.05 was considered significant. Receiver operating characteristic (ROC) curves were generated with an area under the curve (AUC) calculated for each ROC 34 with the best thresholds for group discrimination defined using Youden’s method. 35 All analyses were performed in R v. 4.0.0 with the base and stats packages while ROC analyses...
were performed using the pROC package. More detailed information can be found in the Supplementary Material 1.

RESULTS

732 FDG PET-CT examinations performed during spring 2020; 24 (3.3%) examinations had incidental pulmonary findings suspicious for asymptomatic COVID-19 infection. Nine patients had RT-PCR confirmation of COVID-19 infection (range 0–22 days from scanning), i.e., confirmed cases, and 15 remained suspected cases; these together comprised the COVID-19 group. Twelve out of 15 suspected cases self-isolated at home without access to RT-PCR testing in the community (Table 1, Supplementary Table 1). There were 96 matched control cases; 20 of which had visible areas of GGO/consolidation eligible for SUV_{max} and TBR analysis. A total of 120 anonymised examinations were independently reviewed and analysed (FDG injection: 329±24 MBq).

Table 2. Categorisation of pulmonary findings using the BSTI classification between two reporters

| REPORTER 1 | BSTI 1 | BSTI 2 | BSTI 3 | BSTI 4 | TOTAL |
|------------|--------|--------|--------|--------|-------|
| REPORTER 2 | BSTI 1 | 12     | 2      | 0      | 0     | 14    |
|            | BSTI 2 | 1      | 5      | 2      | 0     | 8     |
|            | BSTI 3 | 0      | 2      | 20     | 0     | 22    |
|            | BSTI 4 | 0      | 0      | 0      | 76    | 76    |
| TOTAL      | 13     | 9      | 22     | 0      | 120   |

BSTI 1, classic/probable COVID-19; BSTI 3, non-COVID-19; BSTI, British Society of Thoracic Imaging; BSTI 2, indeterminate COVID-19; BSTI 4, normal.

Table 3. Association of SUV_{max}, GGO/consolidation by COVID-19 status and BSTI classification

| GROUP               | N  | Minimum | Median | Maximum | Mean | SD  |
|---------------------|----|---------|--------|---------|------|-----|
| CONFIRMED           | 9  | 1.4     | 6      | 8.7     | 5.9  | 2.2 |
| SUSPECTED           | 15 | 0.7     | 3.8    | 7.2     | 4.1  | 1.9 |
| CONTROL             | 20 | 1.1     | 1.9    | 3.8     | 2.1  | 0.7 |
| COVID-19            | 24 | 0.7     | 4.6    | 8.7     | 4.7  | 2.2 |
| BSTI 1              | 13 | 2       | 6      | 8.7     | 5.6  | 2.1 |
| BSTI 2              | 7  | 3.2     | 3.8    | 6.1     | 4.3  | 1.1 |
| BSTI 3              | 24 | 0.7     | 1.9    | 7       | 2.2  | 1.2 |
| BSTI 1 & 2          | 20 | 2       | 5.3    | 8.7     | 5.1  | 1.9 |

GROUP COMPARISON

|                        | UNCORRECTED P-VALUE | FDR   |
|------------------------|---------------------|-------|
| COVID CLASSIFICATION   | <0.0001*            | -     |
| KRUSKAL-WALLIS         |                     |       |
| BSTI CLASSIFICATION    | <0.00001*           | -     |
| KRUSKAL-WALLIS         |                     |       |
| PAIRWISE COMPARISON    |                     |       |
| CONFIRMED vs SUSPECTED | 0.049*              | 0.056 |
| CONFIRMED vs CONTROL   | 0.00074*            | 0.0012*|
| SUSPECTED vs CONTROL   | 0.00046*            | 0.00092*|
| COVID-19 vs CONTROL    | <0.0001*            | 0.00010*|
| BSTI 1 vs BSTI 2       | 0.088               | 0.088 |
| BSTI 1 vs BSTI 3       | <0.0001*            | 0.00010*|
| BSTI 2 vs BSTI 3       | 0.00061*            | 0.0011*|
| BSTI 1 & 2 vs BSTI 3   | <0.00001*           | <0.0001*|

BSTI, British Society of Thoracic Imaging; FDR, False Discovery Rate; GGO, ground glass opacification; N, number of cases; SD, standard deviation; SUV_{max}, maximum standardised uptake value.

BSTI 1 = classic/probable COVID-19; BSTI 2 = indeterminate COVID-19; BSTI 3 = non-COVID-19; BSTI 4 = confirmed and suspected cases (confirmed = pulmonary findings suspicious of COVID-19 infection on FDG PET-CT and a positive RT-PCR test within 28 days of scanning; suspected = pulmonary findings suspicious of COVID-19 infection on FDG PET-CT but no/negative RT-PCR test within 28 days).

*statistically significant
(range 285–392 MBq), mean uptake time: 63 ± 4.5 min (range 56–78 min)).

BSTI classification
7/9 confirmed and 11/15 suspected cases, were categorised as BSTI 1 or 2 (Figures 1–3), 0/96 control cases were categorised as BSTI 1, and only two control cases categorised as BSTI 2 (Figure 4). 2/9 confirmed cases (Figures 5 and 6) and 4/15 suspected cases were categorised as BSTI 3, whilst the remaining control cases were categorised as BSTI 3 (18/96) or BSTI 4 (76/96) (Figure 7). The BSTI classification had a sensitivity of 75% and specificity of 97.9% for the detection of COVID-19 infection on the CT component of FDG PET-CT, assuming that only BSTI 1 and 2 appearances represent COVID-19 infection.

There was almost perfect agreement (weighted κ = 0.94) between the two reporters using the BSTI classification across all four categories with an overall agreement of 94% (113/120). Excluding BSTI 4, which had 100% agreement (76/76), there remained almost perfect agreement for the BSTI 1–3 categories (weighted κ = 0.83) with an overall agreement of 84% (37/44); cases with disagreement only differed by one category between reporters (Table 2).

SUV\textsubscript{max} and TBR GGO/consolidation
There were highly significant group-wise differences ($p < 0.0001$) across both the COVID-19 and BSTI classifications. Pairwise comparisons across the COVID-19 classification revealed no difference in SUV\textsubscript{max} ($p = 0.056$) or TBR ($p = 0.066$) GGO/consolidation between confirmed vs suspected cases after correction for multiple comparisons. SUV\textsubscript{max} GGO/consolidation was, however, significantly higher in the COVID-19 group (confirmed and suspected cases) vs control cases (4.7 vs 2.1; $p < 0.0001$) as was TBR (2.2 vs 1.0; $p < 0.0001$), (Tables 3 and 4, Figures 8 and 9).

Pairwise comparisons across the BSTI classification revealed no differences in SUV\textsubscript{max} GGO/consolidation ($p = 0.088$) or TBR ($p = 0.064$) between BSTI 1 and 2 cases. SUV\textsubscript{max} GGO/consolidation

| GROUP | N | Minimum | Median | Maximum | Mean | SD |
|-------|---|---------|--------|---------|------|----|
| CONFIRMED | 9 | 0.9 | 2.9 | 1.7 | 2.8 | 1.1 |
| SUSPECTED | 14 | 0.7 | 1.7 | 3.4 | 1.9 | 0.9 |
| CONTROL | 19 | 0.4 | 0.9 | 1.7 | 1.0 | 0.3 |
| COVID-19 | 23 | 0.7 | 2.4 | 4.3 | 2.2 | 1.1 |
| BSTI 1 | 13 | 0.7 | 3.0 | 4.3 | 2.7 | 1.1 |
| BSTI 2 | 7 | 1.2 | 1.7 | 2.6 | 1.8 | 0.6 |
| BSTI 3 | 22 | 0.4 | 0.9 | 2.4 | 1.0 | 0.4 |
| BSTI 1 & 2 | 20 | 0.7 | 2.6 | 4.3 | 2.4 | 1.1 |

| GROUP COMPARISON | UNCORRECTED P-VALUE | FDR |
|------------------|----------------------|-----|
| COVID CLASSIFICATION KRUSKAL-WALLIS | $<0.0001^*$ | - |
| BSTI CLASSIFICATION KRUSKAL-WALLIS | $<0.0001^*$ | - |

| PAIRWISE COMPARISON | UNCORRECTED P-VALUE | FDR |
|---------------------|----------------------|-----|
| CONFIRMED vs SUSPECTED | 0.062 | 0.066 |
| CONFIRMED vs CONTROL | $<0.001^*$ | 0.0015$^*$ |
| SUSPECTED vs CONTROL | 0.0012$^*$ | 0.0016$^*$ |
| COVID-19 vs CONTROL | $<0.001^*$ | 0.0001$^*$ |
| BSTI 1 vs BSTI 2 | 0.056 | 0.064 |
| BSTI 1 vs BSTI 3 | 0.00011$^*$ | 0.00025$^*$ |
| BSTI 2 vs BSTI 3 | 0.00093$^*$ | 0.0014$^*$ |
| BSTI 1 & 2 vs BSTI 3 | $<0.0001^*$ | 0.0001$^*$ |

BSTI, British Society of Thoracic Imaging; FDR, False Discovery Rate; GGO, ground glass opacification; N, number of cases; SD, standard deviation; SUV\textsubscript{max}, maximum standardised uptake value.

BSTI 1 = classic/probable COVID-19; BSTI 2 = indeterminate COVID-19; BSTI 3 = non-COVID-19, COVID-19 group = confirmed and suspected cases (confirmed = pulmonary findings suspicious of COVID-19 infection on FDG PET-CT and a positive RT-PCR test within 28 days of scanning; suspected = pulmonary findings suspicious of COVID-19 infection on FDG PET-CT but no/negative RT-PCR test within 28 days)

| Statistically significant |
|--------------------------|
| Hepatic disease involvement precluded liver SUV\textsubscript{mean} measurement and resultant TBR calculation in a single suspected case and single control case; |

Table 4. Association of TBR GGO/consolidation grouped by COVID-19 status and BSTI

| GROUP | N | Minimum | Median | Maximum | Mean | SD |
|-------|---|---------|--------|---------|------|----|
| CONFIRMED | 9 | 0.9 | 2.9 | 1.7 | 2.8 | 1.1 |
| SUSPECTED | 14 | 0.7 | 1.7 | 3.4 | 1.9 | 0.9 |
| CONTROL | 19 | 0.4 | 0.9 | 1.7 | 1.0 | 0.3 |
| COVID-19 | 23 | 0.7 | 2.4 | 4.3 | 2.2 | 1.1 |
| BSTI 1 | 13 | 0.7 | 3.0 | 4.3 | 2.7 | 1.1 |
| BSTI 2 | 7 | 1.2 | 1.7 | 2.6 | 1.8 | 0.6 |
| BSTI 3 | 22 | 0.4 | 0.9 | 2.4 | 1.0 | 0.4 |
| BSTI 1 & 2 | 20 | 0.7 | 2.6 | 4.3 | 2.4 | 1.1 |

| GROUP COMPARISON | UNCORRECTED P-VALUE | FDR |
|------------------|----------------------|-----|
| COVID CLASSIFICATION KRUSKAL-WALLIS | $<0.0001^*$ | - |
| BSTI CLASSIFICATION KRUSKAL-WALLIS | $<0.0001^*$ | - |

| PAIRWISE COMPARISON | UNCORRECTED P-VALUE | FDR |
|---------------------|----------------------|-----|
| CONFIRMED vs SUSPECTED | 0.062 | 0.066 |
| CONFIRMED vs CONTROL | $<0.001^*$ | 0.0015$^*$ |
| SUSPECTED vs CONTROL | 0.0012$^*$ | 0.0016$^*$ |
| COVID-19 vs CONTROL | $<0.001^*$ | 0.0001$^*$ |
| BSTI 1 vs BSTI 2 | 0.056 | 0.064 |
| BSTI 1 vs BSTI 3 | 0.00011$^*$ | 0.00025$^*$ |
| BSTI 2 vs BSTI 3 | 0.00093$^*$ | 0.0014$^*$ |
| BSTI 1 & 2 vs BSTI 3 | $<0.0001^*$ | 0.0001$^*$ |
was however significantly higher in the BSTI 1 & 2 group vs BSTI 3 cases (5.1 vs 2.2; \(p < 0.0001\)) as was TBR (2.4 vs 1.0; \(p < 0.0001\)) (Tables 3 and 4, Figures 8 and 9).

**SUV\textsubscript{max} GGO/consolidation ROC analysis**

ROC curves indicated excellent discrimination using SUV\textsubscript{max} GGO/consolidation with an AUC of 0.93 (0.84–1.00) for differentiating between the BSTI 1 & 2 group and BSTI 3 cases and 0.87 (0.75–0.99) between the COVID-19 group and control cases (Figure 10). Using a SUV\textsubscript{max} 3.15 cut-off, discrimination between the BSTI 1 & 2 group and BSTI 3 cases was achievable with a sensitivity of 0.90 and specificity of 0.88, whilst a SUV\textsubscript{max} 3.45 cut-off enabled discrimination between the COVID-19 group and control cases with a sensitivity of 0.75 and specificity of 0.95.

**SUV metrics in pulmonary and extrapulmonary sites**

There were significantly higher SUV metrics \((p < 0.05)\) in the COVID-19 group vs control cases in 9/15 regions; 3/6 pulmonary regions (right mid zone, right lower zone, left lower zone), 5/6 nodal regions (bilateral hilar, bilateral paratracheal and subcarinal mediastinal nodal stations) and in the spleen. There was no significant difference in SUV\textsubscript{mean} in the liver or bone marrow (Supplementary Table 2, Supplementary Figure 1).

**DISCUSSION**

3.3% (24/732) of FDG PET-CT examinations performed during spring 2020 had incidental pulmonary findings suspicious of asymptomatic COVID-19 infection, which is within the quoted incidence range (2.1–16.2%) from a systematic review of 11 studies.\\(^36\\) Our incidence is lower than reported in a study from a similar sized London institution (9.4%),\(^19\\) but this may be related to potential false-positive observations secondary to unilateral rather bilateral pulmonary findings, i.e., indeterminate for COVID-19 (BSTI 2) coupled with most of their cases with thoracic findings on PET-CT, either negative (4/15) or without RT-PCR confirmation (10/15).

Blinded consensus pulmonary analysis performed 6 months later, with a greater experience of reporting COVID-19 infection on FDG PET-CT, categorised 18/24 of the confirmed and suspected cases as either BSTI 1 (classic/probable COVID-19) or BSTI 2 (indeterminate for COVID-19) coupled with most of their cases with thoracic findings on PET-CT, either negative (4/15) or without RT-PCR confirmation (10/15).

Severa studies report an increased incidence of pulmonary findings suspicious for COVID-19 infection during the ‘first wave’
compared to control cases\textsuperscript{20-22,24} similar to ours, except that patterns compatible with COVID-19 interstitial pneumonia were observed in their control cohorts; this is likely due to the presence of COVID-19 mimics on FDG PET-CT, e.g., influenza pneumonia or OP related to connective tissue disease or drug toxicity. However, most studies did not use a standardised CT grading system for categorising pulmonary changes, likely reducing specificity. Maurea et al\textsuperscript{20} using the COVID-19 Reporting and Data System (CORADS)\textsuperscript{37} reported 14/335 (4\%) control cases with ‘abnormal PET-CT findings suspicious for

Figure 9. Scatter and box plots demonstrating differences in TBR GGO/consolidation across the COVID-19 (confirmed vs suspected vs control) and BSTI classifications (BSTI vs BSTI 2 vs BSTI 3) including aggregated groupings, COVID-19 and BSTI 1 & 2 (▲=CONFIRMED, ●=SUSPECTED, ■=CONTROL cases). Thick horizontal solid bar across the box shows the median, box height shows interquartile range (25-75th percentiles) and whiskers show minimum and maximum values.

Figure 10. ROC curves determining the diagnostic performance of SUV\textsubscript{max} GGO/consolidation on FDG PET-CT using the aggregated groupings COVID-19 group vs control cases and BSTI 1 & 2 group vs BSTI 3 cases.
COVID-19 infection. However, 9/14 (64%) were classified as CO-RADS 2 (CT abnormalities consistent infection other than COVID-19) or CO-RADS 3 (uncertain CT findings for COVID-19) suggesting an overestimation of PET-CT findings suspicious for COVID-19 infection in their control population.

Our study, the first to formally assess agreement between two reporters using the BSTI classification on FDG PET-CT, demonstrated almost perfect agreement (weighted \( \kappa = 0.94 \)) when compared to the published COVID-19 CT reporting proforma. Inui et al. compared different CT grading systems for COVID-19 infection, and showed that all had reasonable diagnostic performance (0.80–0.84), albeit with lower interobserver agreement (Cohen \( \kappa = 0.61–0.63 \)) than ours, but that CO-RADS and BSTI outperformed the other two classifications. Our higher interobserver agreement may be augmented by amalgamation of the ‘classic’ and ‘probable’ COVID-19 categories to represent BSTI 1 as per the published COVID-19 CT reporting proforma rather than interpretate them as two separate categories. The inadequacies of the low-dose non-breath hold CT component of a PET-CT examination, requiring a more pragmatic approach to assessing the lungs, i.e., forgoing subtleties, also likely contributed to more consistent and reproducible observations.

FDG uptake in areas of GGO/consolidation was significantly higher in the COVID-19 group vs control cases (SUV\(_{\text{max}}\) 4.7 vs 2.1) and BSTI 1 & 2 group vs BSTI 3 cases (SUV\(_{\text{max}}\) 5.1 vs 2.2); similar values have been reported in an early systematic review of incidental COVID-19 infection on FDG PET-CT (mean SUV\(_{\text{max}}\) 4.9). Italian multicentre study (mean SUV\(_{\text{max}}\) 4.1)) TBR analysis demonstrated that the intensity of FDG uptake in GGO/consolidation was \( \times 2 \) liver SUV\(_{\text{mean}}\) in the COVID-19 and BSTI 1 & 2 groups, and lower and comparable to liver SUV\(_{\text{mean}}\) for control and BSTI 3 cases. These findings confirm that a distinctive feature of COVID-19 infection is the association of high FDG uptake with areas of GGO/consolidation, related to multienucleated giant cells and focal clusters of lymphomonocytic infiltration in the context of diffuse alveolar damage, demonstrable even in early COVID-19 infection.

The discriminative ability of SUV\(_{\text{max}}\) in areas of GGO/consolidation to differentiate between the BSTI 1 & 2 group and BSTI 3 cases was high; using a SUV\(_{\text{max}}\) 3.15 cut-off, discrimination between BSTI 1 & 2 group and BSTI 3 cases was achievable with high sensitivity and specificity. From a clinical viewpoint, pulmonary findings compatible with classic/probable COVID-19 (BSTI 1), e.g., basilar peripheral GGO/consolidation with a reverse-halo or peribronchial opacity, i.e., OP pattern, or indeterminate COVID-19 (BSTI 2), e.g., unilateral, non-peripheral GGO/consolidation, are likely to have higher levels of associated FDG uptake (SUV\(_{\text{max}}\) >3.15) in comparison with GGO/consolidation in a non-COVID-19 (BSTI 3) pattern.

Our study reaffirms that the low-dose non-breath hold CT component of the study can enable diagnosis despite not being of ‘diagnostic quality’ and is not solely for the purposes of attenuation correction and localisation. The absence of a full inspiratory effort and breathing artefact during scanning can limit accuracy, however. Difficulty in detection/characterisation of smaller lesions particularly towards the lung bases limits sensitivity, whilst an increased incidence of dependent GGO alongside areas of basal atelectasis, can be potentially misinterpreted as significant pathology, reducing specificity. Unrelated pulmonary pathologies, e.g., other viral pneumonias, OP secondary to connective tissue disease or drug toxicity or active pulmonary fibrosis can have similar appearances to COVID-19 infection, and will reduce specificity, although in our study this was only encountered in 2/96 control cases (Figure 4).

We found significantly higher SUV metrics in the COVID-19 group vs control cases in the mid-lower lung zones, both hilar and central mediastinal nodal stations, and spleen, suggesting the presence of generalised background inflammation. Lower zone predominant background pulmonary inflammation correlates with the tendency of COVID-19 infection to present with bilateral abnormalities affecting both lower lobes. FDG avid intrathoracic and supraclavicular nodes with COVID-19 infection have been reported in several studies with varied frequency, with or without CT enlargement whilst only one study has reported increased splenic uptake (5/13 patients) and increased bone marrow uptake; extrapulmonary abnormalities involving the salivary glands and gastro-intestinal tract were not routinely assessed for during our study. The presence of generalised systemic inflammation has been confirmed in small cohorts of patients recovering from COVID-19 infection (lungs, mediastinal nodes, spleen, liver, large vessels) as well as in patients with post-COVID syndrome in conjunction with findings of brain hypometabolism.

The major limitation to our study, common to many, is the absence of RT-PCR testing for all FDG PET-CT examinations during spring 2020, due to a lack of testing capacity. Patients with COVID-19 infection but without pulmonary findings suspicious of infection will have been missed using our methodology, which will undoubtedly affect the sensitivity and specificity estimate of the BSTI classification on FDG PET-CT. In addition, this limitation also brings into question the classification of suspected cases which had either no (12/15) or a negative (3/15) RT-PCR test despite the presence of pulmonary findings suspicious of COVID-19 infection on FDG PET-CT (Supplementary Table 1). However, SUV\(_{\text{max}}\) GGO/consolidation and TBR analysis demonstrated that confirmed and suspected cases were similar to each other but were individually as well as in combination (COVID-19 group), distinct from control cases, supporting our methodology of combining these cases for analysis (Tables 3 and 4, Figures 8 and 9). In addition, the sensitivity of the gold standard nasopharyngeal RT-PCR in asymptomatic individuals is not 100% and is lower in asymptomatic individuals, i.e., higher false-negative rates. Sensitivity can be improved through repeat RT-PCR testing or with bronchoalveolar lavage; a study of 46 patients reported 18 patients (39%) had a positive bronchoalveolar lavage RT-PCR despite two preceding negative nasopharyngeal RT-PCR tests with importantly 13 of these 18 patients (72%) with two preceding negative nasopharyngeal RT-PCR tests having CT findings compatible with COVID-19 infection. This confirms the imperfection of single/multiple nasopharyngeal RT-PCR testing.
tests and that pulmonary changes compatible with COVID-19 infection in the context of a negative RT-PCR test(s) cannot be readily dismissed.

**CONCLUSION**

Asymptomatic COVID-19 infection on FDG PET-CT is characterised by bilateral areas of GGO/consolidation that are associated with increased FDG uptake (>2x liver SUV$_{\text{mean}}$) and which can be identified with high reproducibility using the BSTI classification. These changes occur on the background of generalised inflammation within the mid-lower zones of the lungs, hilar and central mediastinal nodal stations, and spleen. This analysis will enable better preparedness for identification of asymptomatic COVID-19 infection on FDG PET-CT, prompting early confirmation RT-PCR testing, and minimising the risk of undetected infection to both the individual and society as a whole.

**AVAILABILITY OF DATA AND MATERIALS:** Anonymised data that supports these findings are available from the corresponding author upon reasonable request.

**ACKNOWLEDGMENT**

This work is supported by the Wellcome EPSRC Centre for Medical Engineering at King’s College London (WT 203148/Z/16/Z) and the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy’s & St Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust. SFB acknowledges support from the National Institute for Health Research and Social Care (NIHR) [RP-2-16-07-001]. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

The authors would like to thank the whole team at the King’s College London & Guy’s and St. Thomas’ PET Centre for their efforts during the COVID-19 pandemic and continuing professionalism, hard work and dedication.

**CONFLICTS OF INTERESTS**

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**AVAILABILITY OF DATA AND MATERIALS**

Anonymised data that supports these findings are available from the corresponding author upon reasonable request.

**REFERENCES**

1. Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, et al. SARS-cov-2 transmission from people without covid-19 symptoms. *JAMA Netw Open* January 4, 2021; 4: e2035057. https://doi.org/10.1001/jamanetworkopen.2020.35057
2. Butler-Laporte G, Lawandi A, Schiller I, Yao M, Dedukuri N, McDonald EG, et al. Comparison of saliva and nasopharyngeal swab nucleic acid amplification testing for detection of sars-cov-2: a systematic review and meta-analysis. *JAMA Intern Med* March 1, 2021; 181: 353–60. https://doi.org/10.1001/jamainternmed.2020.8876
3. Tsang NNY, So HC, Ng KY, Cowling BJ, Leung GM, Ip DKM. Diagnostic performance of different sampling approaches for sars-cov-2 rt-PCR testing: a systematic review and meta-analysis. *Lancet Infect Dis* September 21, 2020; 21: S1473-3099(21)00146-8: 1233–45. https://doi.org/10.1016/S1473-3099(21)00146-8
4. Ridgway JP, Pisanj J, Landon E, Beavis KG, Robicsek A. Clinical sensitivity of severe acute respiratory syndrome coronavirus 2 nucleic acid amplification tests for diagnosing coronavirus disease 2019. *Open Forum Infect Dis* 2020; 7: ofaa315. https://doi.org/10.1093/ofid/ofaa315
5. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for sars-cov-2. *JAMA* 9, 2020; 323: 2249–51. https://doi.org/10.1001/jama.2020.8259
6. Mallett S, Allen AJ, Graziano S, Taylor SA, Sakai NS, Green K, et al. At what times during infection is sars-cov-2 detectable and no longer detectable using rt-pcr-based tests? a systematic review of individual participant data. *BMC Med* November 4, 2020; 18(1): 346. https://doi.org/10.1186/s12916-020-01810-8
7. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest ct for covid-19: comparison to rt-pcr. *Radiology* August 2020; 296: E115–17. https://doi.org/10.1148/radiol.2020020432
8. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest ct and rt-pcr testing for coronavirus disease 2019 (covid-19) in china: a report of 1014 cases. *Radiology* August 2020; 296: E32–40. https://doi.org/10.1148/radiol.2020200842
9. Raptis CA, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, et al. Chest ct and coronavirus disease (covid-19): a critical review of the literature to date. *AJR Am J Roentgenol* October 2020; 215: 839–42. https://doi.org/10.2214/AJR.20.23202
10. Nair A, Rodrigues JCL, Hare S, Edey A, Devaraj A, Jacob J, et al. A british society of thoracic imaging statement: considerations in designing local imaging diagnostic algorithms for the covid-19 pandemic. *Clin Radiol* May 2020; 75: S0009-9266(20)30096-9: 329–34. https://doi.org/10.1016/j.crad.2020.03.008
11. Park JY, Freer R, Stevens R, Soneji N, Jones N. The accuracy of chest ct in the diagnosis of COVID-19: An umbrella review. 2021. Available from: https://www.cebm.net/ covid-19/the-accuracy-of-ct-ct-in-the-diagnosis-of-covid-19-an-umbrella-review/
12. British Society of Thoracic Imaging. Covid-19 BSTI reporting templates. 2020. Available from: https://www.bssti.org.uk/ covid-19-resources/covid-19-bsti-reporting-templates/
13. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with covid-19 pneumonia in wuhan, china: a descriptive study. *Lancet Infect Dis* April 2020; 20: S1473-3099(20)30086-4: 425–34. https://doi.org/10.1016/S1473-3099(20)30086-4
14. Zhang R, Ouyang H, Fu L, Wang S, Han J, Huang K, et al. CT features of sars-cov-2 pneumonia according to clinical presentation: a retrospective analysis of 120
Incidental asymptomatic COVID-19 infection on FDG PET-CT

15. Inui S, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, et al. Chest CT Findings in Cases from the Cruise Ship Diamond Princess with Coronavirus Disease (COVID-19). Radiology. Cardiothoracic imaging. Vol. 2; 2020., pp. e201110. https://doi.org/10.1148/rct.20202001110

16. Qin C, Liu F, Yen TC, Lan X. 18F-fdg pet/ct findings of covid-19: a series of four highly suspected cases. Eur J Nucl Med Mol Imaging May 2020; 47: 1281–86. https://doi.org/10.1007/s00259-020-04734-w

17. Zou S, Zhu X. FDG pet/ct of covid-19. Radiology August 2020; 296(2): E118. https://doi.org/10.1148/radiol.2020200770

18. Kidane B, Levin DP. Identification and resolution of asymptomatic covid-19 pneumonitis and colitis: serial assessment of fluorodeoxyglucose positron emission tomography-computed tomography for evaluation of lung cancer. J Thorac Oncol January 2021; 16: S1556-0864(20)30725-5: e1–3. https://doi.org/10.1016/j.jtho.2020.09.004

19. Halsey R, Priftakis D, Mackenzie S, Wan S, Davis LM, Lilburn D, et al. COVID-19 in the act: incidental 18F-fdg pet/ct findings in asymptomatic patients and those with symptoms not primarily correlated with covid-19 during the united kingdom coronavirus lockdown. Eur J Nucl Med Imaging January 2021; 48: 269–81. https://doi.org/10.1007/s00259-020-04972-y

20. Maurea S, Mainolfi CG, Bombace C, Annunziata A, Attanasio L, Petretta M, et al. FDG-pet/ct imaging during the covid-19 emergency: a southern italian perspective. Eur J Nucl Med Imaging October 2020; 47: 2691–97. https://doi.org/10.1007/s00259-020-04931-7

21. Pellaridy A, Rousseau C, Labbe C, Liberge R, Bodet-Milin C, Kraebel-Bodere F, et al. Incidental findings suggestive of covid-19 in asymptomatic cancer patients undergoing 18F-fdg pet/ct in a low prevalence region. Eur J Nucl Med Imaging January 2021; 48: 287–92. https://doi.org/10.1007/s00259-020-05014-3

22. Setti L, Bonacina M, Meroni R, Kirienko M, Galli F, Dalto SC, et al. Increased incidence of interstitial pneumonia detected on [18F]-fdg-pet/ct in asymptomatic cancer patients during covid-19 pandemic in lombardy: a casuality or covid-19 infection? Eur J Nucl Med Imaging March 2021; 48: 777–85. https://doi.org/10.1007/s00259-020-05027-y

23. Wąskie-Corich CG, Blanes García AM, Ferrando-Castagneto F, Valhondo-Rama R, Ortega Candí A, Rodríguez Rey C, et al. Assessment of extra-parenchymal lung involvement in asymptomatic cancer patients with covid-19 pneumonia detected on 18F-fdg pet-ct studies. Eur J Nucl Med Imaging March 2021; 48: 768–76. https://doi.org/10.1007/s00259-020-05195-y

24. Alboano D, Bertagana F, Alongi P, Baldari S, Baldoncini A, Bartolomei M, et al. Prevalence of interstitial pneumonia suggestive of covid-19 at 18F-fdg pet/ct in oncological asymptomatic patients in a high prevalence country during pandemic period: a national multi-centric retrospective study. Eur J Nucl Med Mol Imaging August 2021; 48: 2871–82. https://doi.org/10.1007/s00259-021-05219-0

25. Dietz M, Chironi G, Claessens Y-E, Farhad RL, Rouquette I, Serrano B, et al. COVID-19 pneumonia: relationship between inflammation assessed by whole-body fdg pet/ct and short-term clinical outcome. Eur J Nucl Med Imaging January 2021; 48: 260–68. https://doi.org/10.1007/s00259-020-04968-8

26. Deng Y, Lei L, Chen Y, Zhang W. The potential added value of fdg pet/ct for covid-19 pneumonia. Eur J Nucl Med Imaging July 2020; 47: 1634–35. https://doi.org/10.1007/s00259-020-04767-1

27. Lütje S, Marinova M, Kütting D, Attenberger U, Eissler M, Bundschuh RA. Nuclear medicine in sars-cov-2 pandemia: 18F-fdg- pet/ct to visualize covid-19. Nuklearmedizin 2020; 59: 276–80. https://doi.org/10.1055/a-1152-2341

28. Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M, et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. Eur J Cancer November 2020; 139: S0959-8049(20)30462-7: 43–50. https://doi.org/10.1016/jejca.2020.08.011

29. Lee LYW, Cazier J-B, Starkey T, Briggs SEW, Arnold R, Bish V, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol October 2020; 21: S1470-2245(20)30442-3: 1309–16. https://doi.org/10.1016/S1470-2245(20)30442-3

30. Iacobucci G. Covid-19: lack of capacity led Annunziata S, Delgado Bolton RC, Kamani C-H, Prior JO, Albano D, Bertagana F, et al. Role of 2-[18F]fdg as a radiopharmaceutical for pet/ct in patients with covid-19: a systematic review. Pharmaceuticals (Basel) 10, 2020; 13(11): E377. https://doi.org/10.3390/ph13110377

31. Murphy DJ, Royle L, Chalampalakis Z, Alves RL, Abbott GF, Rice TW. International society guidelines. Radiology August 2020; 296: E97–104. https://doi.org/10.1148/radiol.2020201473

32. Inui S, Kurokawa R, Nakai Y, Watanabe Y, Kurokawa M, Sakurai K, et al. Comparison of chest ct grading systems in coronavirus disease 2019 (covid-19) pneumonia. Radiol Cardiothoracic Imaging 2020; 2: e200492. https://doi.org/10.1148/radiolccr202003106-3.00-e2-3

33. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159–74. https://doi.org/10.2307/2529310

34. Carpenter JV, Pan J, Rai SN, Galanidou S. ROC- ing along: evaluation and interpretation of receiver operating characteristic curves. Surgery June 2016; 159: S0039-6606(16)30066-0: 1638–45. https://doi.org/10.1016/j.surg.2015.12.029

35. YOUNDEN WJ. Index for rating diagnostic tests. Cancer 1950; 3: 32–35. https://doi.org/10.1002/1097-0142(1950)3:1<32::aid-cncr2820303106-3.0.co;2-3

36. Annunziata S, Delgado Bolton RC, Kamani C-H, Prior JO, Albano D, Bertagana F, et al. CO-rads: a categorical ct assessment scheme for patients suspected of having covid-19 definition and evaluation. Radiology August 2020; 296: E97–104. https://doi.org/10.1148/radiol.2020201473

37. Inui S, Kurokawa R, Nakai Y, Watanabe Y, Kurokawa M, Sakurai K, et al. Comparison of chest ct grading systems in coronavirus disease 2019 (covid-19) pneumonia. Semin Nucl Med May 2020; 50(5): 597–600. https://doi.org/10.1016/j.semnuclmed.2020.05.001

38. Inui S, Fujii W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (covid-19) pneumonia in two patients with lung cancer. J Thorac Oncol May 2020; 15: S1556-0864(20)30132-5:
41. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of covid-19 cases from northern italy: a two-centre descriptive study. Lancet Infect Dis October 2020; 20: S1473-3099(20)30434-5: 1135–40; . https://doi.org/10.1016/S1473-3099(20)30434-5

42. Adams HJA, Kwee TC, Yakar D, Hope MD, Kwee RM. Chest ct imaging signature of coronavirus disease 2019 infection: in pursuit of the scientific evidence. Chest November 2020; 158: S0012-3692(20)31733-5: 1885–95; . https://doi.org/10.1016/j.chest.2020.06.025

43. Kwee TC, Kwee RM. Chest ct in covid-19: what the radiologist needs to know. Radiographics 2020; 40: 1848–65. https://doi.org/10.1148/rg.2020200159

44. Bai Y, Xu J, Chen L, Fu C, Kang Y, Zhang W, et al. Inflammatory response in lungs and extrapulmonary sites detected by [18f] fluorodeoxyglucose pet/ct in convalescing covid-19 patients tested negative for coronavirus. Eur J Nucl Med Mol Imaging July 2021; 48: 2531–42. https://doi.org/10.1007/s00259-020-05083-4

45. Sollini M, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, Gelardi F, et al. Vasculitis changes in covid-19 survivors with persistent symptoms: an [18f]fdg-pet/ct study. Eur J Nucl Med Mol Imaging May 2021; 48: 1460–66. https://doi.org/10.1007/s00259-020-05084-3

46. Sollini M, Morbelli S, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, et al. Long covid hallmarks on [18f]fdg-pet/ct: a case-control study. Eur J Nucl Med Mol Imaging September 2021; 48: 3187–97. https://doi.org/10.1007/s00259-021-05294-3

47. Guedj E, Campion JY, Dudouet P, Kaplan E, Bregen F, Tissot-Dupont H, et al. 18F-fdg brain pet hypometabolism in patients with long covid. Eur J Nucl Med Mol Imaging August 2021; 48: 2823–33. https://doi.org/10.1007/s00259-021-05215-4

48. Donegani MI, Miceli A, Pardini M, Bauckneht M, Chiola S, Pennone M, et al. Brain metabolic correlates of persistent olfactory dysfunction after sars-cov2 infection. Biomedicines 12, 2021; 9(3): 287. https://doi.org/10.3390/biomedicines9030287

49. Green DA, Zucker J, Westblade LF, Whittier S, Rennert H, Velu P, et al. Clinical performance of sars-cov-2 molecular tests. J Clin Microbiol 23, 2020; 58(8): e00995-20. https://doi.org/10.1128/JCM.00995-20

50. Patrucco F, Carriero A, Falaschi Z, Paschè A, Gavelli F, Airola C, et al. COVID-19 diagnosis in case of two negative nasopharyngeal swabs: association between chest ct and bronchoalveolar lavage results. Radiology March 2021; 298: E152–55. https://doi.org/10.1148/radiol.2020203776