



Time-related aortic inflammatory response, as assessed with ^{18}F -FDG PET/CT, in patients hospitalized with severely or critical COVID-19: the COVAIR study

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Aim. Arterial involvement has been implicated in the coronavirus disease of 2019 (COVID-19). Fluorine 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) imaging is a valuable tool for the assessment of aortic inflammation and is a predictor of outcome. We sought to prospectively assess the presence of aortic inflammation and its time-dependent trend in patients with COVID-19.

Methods. Between November 2020 and May 2021, in this pilot, case-control study, we recruited 20 patients with severe or critical COVID-19 (mean age of 59 ± 12 years), while 10 age and sex-matched individuals served as the control group. Aortic inflammation was assessed by measuring ^{18}F -FDG uptake in PET/CT performed 20-120 days post-admission. Global aortic target to background ratio (GLA-TBR) was calculated as the sum of TBRs of ascending and descending aorta, aortic arch, and abdominal aorta divided by 4. Index aortic segment TBR (IAS-TBR) was designated as the aortic segment with the highest TBR.

Results. There was no significant difference in aortic ^{18}F -FDG PET/CT uptake between patients and controls (GLA-TBR: 1.46 [1.40-1.57] vs. 1.43 [1.32-1.70], respectively, $P = 0.422$

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and IAS-TBR: 1.60 [1.50-1.67] vs. 1.50 [1.42-1.61], respectively, $P = 0.155$). There was a moderate correlation between aortic TBR values (both GLA and IAS) and time distance from admission to ¹⁸F-FDG PET-CT scan (Spearman's $\rho = -0.528$, $P = 0.017$ and Spearman's $\rho = -0.480$, $p = 0.032$, respectively). Patients who were scanned less than or equal to 60 days from admission ($n = 11$) had significantly higher GLA-TBR values compared to patients that were examined more than 60 days post-admission (GLA-TBR: 1.53 [1.42-1.60] vs. 1.40 [1.33-1.45], respectively, $P = 0.016$ and IAS-TBR: 1.64 [1.51-1.74] vs. 1.52 [1.46-1.60], respectively, $P = 0.038$). There was a significant difference in IAS-TBR between patients scanned ≤ 60 days and controls (1.64 [1.51-1.74] vs. 1.50 [1.41-1.61], $P = 0.036$).

Conclusion. This is the first study suggesting that aortic inflammation, as assessed by ¹⁸F-FDG PET/CT imaging, is increased in the early post COVID phase in patients with severe or critical COVID-19 and largely resolves over time. Our findings may have important implications for the understanding of the course of the disease and for improving our preventive and therapeutic strategies. (J Nucl Cardiol 2022)

Key Words: ¹⁸F-FDG PET/CT • Aortic inflammation • COVID 19 • Cardiovascular risk • Endothelial dysfunction • Long COVID • CRP

INTRODUCTION

The coronavirus disease of 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the result of disruption of the immune, renin-angiotensin-aldosterone (RAA), and thrombotic balance.¹ All these mechanisms converge on vascular dysfunction as a common pathway. The main organs involved in COVID-19, i.e., the lungs, the heart, and the kidneys, exhibit similar findings of endothelial dysfunction and vasculitis with monoclonal cells, lymphocyte infiltration and intravascular thrombosis.² Transient increase of arterial stiffness that is associated with hospital stay length³ attests to the vascular involvement in COVID-19. Nevertheless, the patients that end up with irreversible myocardial damage at long-term follow constitute a small percentage.^{1,4,5}

¹⁸Fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) imaging is a valuable tool for the diagnosis and assessment of disease severity in different types of vascular and cardiac inflammation and infection⁶⁻⁹ and is a potential predictor of outcomes in different settings.^{7,10,11} We have shown that aortic FDG uptake is associated with disease severity and response to treatment in patients with lymphoma and hypercholesterolemia.^{12,13}

There are very few observational studies regarding ¹⁸F-FDG PET/CT in COVID-19 affected patients focusing on the lung FDG uptake.^{14,15} We investigated the effects of COVID-19 on a vascular level, by assessing ¹⁸F-FDG PET/CT uptake in the aorta in patients with severe or critical illness.

METHODS

Between November 2020 and May 2021, we recruited 20 patients from two dedicated COVID 19 hospitalization centers (General Hospital 'Evangelismos' and Thoracic Diseases General Hospital 'Sotiria' in Athens, Greece), who were diagnosed and admitted with severe or critical COVID 19. The criteria for severe COVID 19 were (1) SpO₂ < 94% on room air at sea level, (2) and a respiratory rate > 30 breaths/min, (3) PaO₂/FiO₂ < 300 mmHg or lung infiltrates > 50%. The criteria for critical COVID 19 were the presence of respiratory failure, septic shock, and/or multiple organ dysfunction.¹⁶ Patient inclusion criteria were 1. Positive PCR test for COVID 19, 2. Fulfillment of criteria for severe or critical COVID 19 as described above, 3. age > 18 years old, 4. a given written signed consent form, 5. glucose levels prior to ¹⁸F-FDG PET/CT < 200 mg/dL, 6. to be holders of national insurance number. Exclusion criteria were 1. Age < 18 or > 80 years old, 2. Pregnancy or breastfeeding, 3. Inability to comply with follow up instructions 4. Enrollment in interventional studies. Patients underwent whole body ¹⁸F-FDG PET/CT imaging between 20 to 120 days after hospital admission. Ten age and sex-matched individuals scheduled for ¹⁸F-FDG PET/CT imaging served as the control group. They had a prior history of malignancy but were free of active disease at the time of the ¹⁸F-FDG-PET/CT investigation. Image acquisition was obtained following recommended protocols and as previously described.^{9,17} Patients were classified according to their cardiovascular risk as low, intermediate, high and very high risk for cardiovascular disease as suggested by the

European Society Guidelines on prevention of cardiovascular disease.¹⁸ Patients enrolled in the study had capacity to give informed consent either at the time of admission, or they were enrolled in the study at the time that they were able to give informed consent. No surrogates were recruited to provide consent for the participants. The study was approved by the Institutional Research Ethics Committee and conducted according to institutional guidelines and the Declaration of Helsinki.

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Study outcomes

The primary endpoints of the study were: (1) the difference of aortic inflammation as assessed by ^{18}F -FDG PET/CT between patients with recent COVID 19 and control subjects and (2) the association of aortic FDG uptake with time after admission in order to investigate the behavior of aortic inflammation over time post COVID 19. The secondary outcome was to investigate the association between aortic FDG uptake and disease severity biomarkers. In a post hoc analysis, we compared aortic FDG uptake in patients in early (≤ 60 days from admission) or late (> 60 days from admission) recovery phase vs. aortic FDG uptake in control subjects.

^{18}F -FDG PET/CT imaging protocol

Image acquisition was obtained following recommended protocols and as previously described. None of the patients had blood glucose levels $> 200 \text{ mg dL}^{-1}$ before injection. FDG was injected intravenously (3-4 MBq/kg) and scanning was performed at 60-120 minutes post-injection for aortic tracer uptake assessment. A low dose CT scan in a supine position was obtained for attenuation correction and image fusion. No CT intravenous (IV) contrast was administered. PET data were reconstructed using an ordered subset expectation maximization iterative reconstruction algorithm. Regions of interest (ROI) around the aortic wall were manually drawn along the entire aorta in consecutive axial slices at intervals of 5 mm. Metabolic activity within each arterial ROI was measured by maximum standardized uptake value (SUV_{max}). Six consecutive circular ROIs of 3 mm diameter, were drawn within the superior vena cava and an average venous SUV_{mean} value was calculated. The arterial target to background ratio (TBR) was then derived by dividing the mean aortic SUV_{max} to the average value of venous SUV_{mean} . Finally, global aortic TBR (GLA-TBR) was calculated

as the sum of TBRs of ascending and descending aorta, aortic arch, and abdominal aorta divided by 4. Index aortic segment TBR (IAS-TBR) was designated as the aortic segment with the highest TBR.

Blood measurements

Blood samples from the 20 COVID-19 patients were obtained < 48 hours after admission. On each blood sample, high sensitivity troponin I (hs-Troponin I) and CRP (hs-CRP) were measured in the serum. hsCRP and hs-Troponin I were promptly available from the laboratory results of the 2 hospitals.

Statistical analysis

Quantitative data are presented as mean values \pm standard deviation (SD) or medians (interquartile range), while qualitative variables as absolute and relative frequencies. Parameters which exhibited a non-normally distribution were presented as the median (25th-75th percentile).

For between-groups comparisons, the Student's t -test or χ^2 test for continuous and categorical variables, respectively, were employed. For comparison of TBR values, Mann Whitney U test was performed. To assess the relation between aortic TBR and inflammatory markers, time distance since admission D-dimers and oxygen saturation (SO_2), Spearman's rho was employed. Linear regression analysis was performed using aortic TBR as the dependent variable and time distance from admission, age, sex and systematic inflammation as described by hs-CRP as covariates.¹⁹ Further linear regression analysis was performed using aortic TBR as the dependent variable and time distance from admission, age, sex and CVD risk according to European Society of Cardiology (ESC) guidelines as covariates (Supplementary material).

A two-tailed P -value < 0.05 was considered significant. All statistical analyses were performed with the SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Mean age of patients was 59 ± 12 years and 10 were males (60%). Ten patients had hypertension (50%), six had dyslipidemia (30%) and 6 were diabetics (30%). There were 6 smokers (60%) in the patient group. Six patients were on statins, six on angiotensin receptor blockers (ARBs) and one on aspirin (Table 1).

There was a moderate association between aortic TBR values (both GLA and IAS) and time distance from admission to ^{18}F -FDG PET-CT scan (Spearman's rho = -0.528 , $P = 0.017$ and Spearman's rho = -0.480 ,

Table 1. Sociodemographic and clinical characteristics of patients (n = 20) and age and sex-matched control subjects (n = 10)

	Patients (n = 20)	Controls (n = 10)	P-value
Age	59.3 (± 12.2)	55.3 (± 15.2)	0.500
Male	60% (n = 12)	60% (n = 6)	1.0
Obesity*	10% (n = 2)	n/a	-
Medication during hospitalization			
Steroids	100% (n = 20)	-	-
Remdesivir	80% (n = 16)	-	-
COVID 19 severity indicators			
SO ₂ on admission (%)	90 (± 5)	-	-
Respiratory rate on admission (bpm)	27.12 (± 6.26)	-	-
Admission to ICU	65% (n = 13)	-	-
Hospitalization days	19.7 (± 11.6)	-	-
Biomarkers on admission			
hs-CRP (mg/L)	9.77 (3.78-14.25)	-	-
hs-Troponin I (ng/L)	6.50 (4.17-9.01)	-	-
D-dimers (mg/L)	1.085 (0.59-2.02)	-	-
Target to blood ratio (TBR)**			
Global Aortic TBR	1.46 (1.40-1.57)	1.43 (1.28-1.64)	0.422
Index aortic segment TBR***	1.60 (1.50-1.67)	1.50 (1.42-1.61)	0.155
Ascending aorta TBR	1.50 (1.45-1.65)	1.41 (1.33-1.61)	0.150
Aortic arch TBR	1.48 (1.42-1.53)	1.41 (1.34-1.54)	0.218
Descending thoracic aorta TBR	1.41 (1.30-1.49)	1.38 (1.23-1.48)	0.566
Abdominal aorta TBR	1.37 (1.29-1.62)	1.40 (1.32-1.51)	0.897

Categorical variables are presented as absolute and relative frequencies, while continuous variables as mean value ± SD for normally distributed and median value (25th-75th percentile) for skewed variables. χ^2 test was employed for between group comparisons of categorical variables, *t*-test for normally distributed continuous variables and *BMI > 30 kg/m²

**Mann Whitney *U* test was performed for comparison of aortic TBR values.

***Index aortic segment was determined as the aortic segment with the higher TBR value

Bpm, breaths per minute; *CVD*, cardiovascular disease; *FHx*, family History; *CAD*, coronary artery disease; *ICU*, intensive care unit; *hs-CRP*, high sensitivity C reactive protein; *SD*, Standard deviation; *SO₂*, Oxygen saturation

$P = 0.032$, respectively) (Figure 1). Multivariate analysis showed that both GLA and IAS-TBR remained moderately associated with time distance from admission to ¹⁸F-FDG PET/CT and with systemic inflammation assessed by hs-CRP, even after adjustment for sex and age (Tables 2 and 3). A multivariate analysis associating GLA and IAS-TBR with time distance from COVID 19 admission, using cardiovascular risk, age and sex as confounders is presented in the Supplement Tables 1 and 2, respectively.

There was no significant difference in aortic ¹⁸F-FDG PET/CT uptake between patients and controls (GLA-TBR_{patients} = 1.46 [1.40-1.57] vs. GLA-TBR_{control} = 1.43 [1.32-1.70], respectively, $P = 0.422$). Similarly, there was no difference in IAS-TBR (IAS-TBR_{patients} = 1.60 [1.50-1.67] vs. IAS-TBR_{control} = 1.50 [1.42-1.61], $P = 0.155$).

The median (interquartile range) time from admission to the ¹⁸F-FDG PET/CT was 58.5 (45-74) days. Patients who were scanned less than or equal to 60 days from admission (n = 11) had significantly higher GLA-TBR values compared to patients that were examined more than 60 days post-admission (GLA-TBR_{≤60 days} = 1.53 [1.42-1.60] vs. GLA-TBR_{>60 days} = 1.40 [1.33-1.45], $P = 0.016$). Similarly, using IAS for comparison of patients scanned less than or equal to 60 days with patients scanned more than 60 days revealed significantly higher values in the first group (IAS-TBR_{≤60 days} = 1.64 [1.51-1.74], IAS-TBR_{>60 days} = 1.52 [1.46-1.60], $P = 0.038$). These 11 patients scanned ≤ 60 days from admission, were also compared to controls and while there was not a statistically significant difference, there was a trend towards higher values of the patients scanned ≤ 60 days from admission compared with

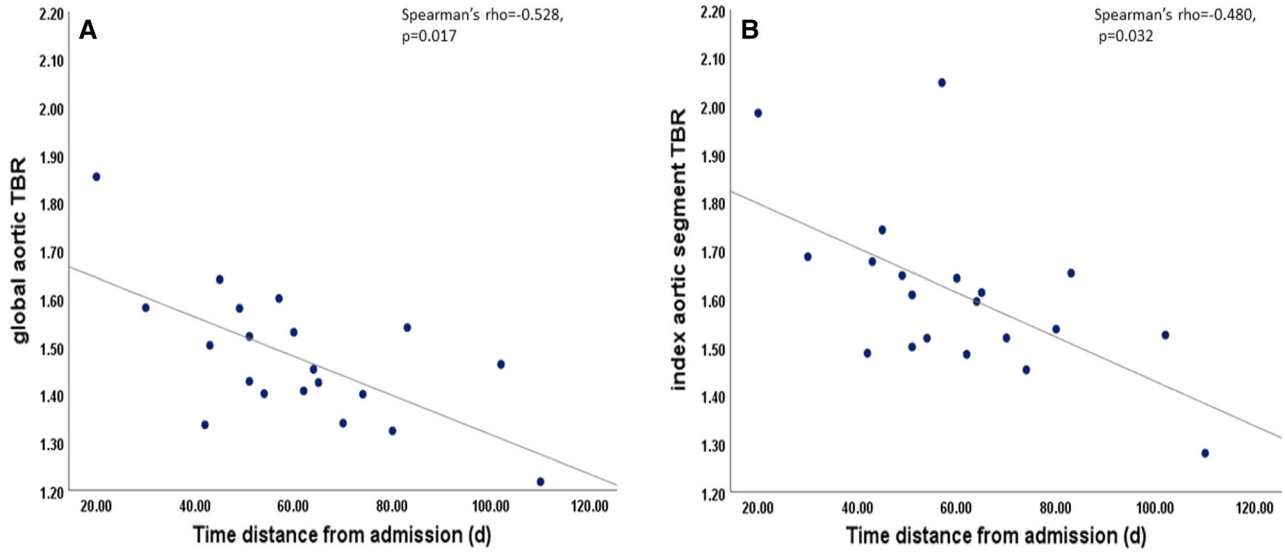


Figure 1. Association between aortic TBR values and time distance from admission to ¹⁸F-FDG PET/CT scan. **A** Moderate negative association of GLA-TBR values with time from admission for COVID 19 (Spearman’s rho – 0.528, P = 0.017). **B** Moderate negative association of IAS-TBR with time from admission for COVID 19 (Spearman’s rho = – 0.480, P = 0.032). *d*, days; *TBR*, target to background ratio; ¹⁸F-FDG PET/CT, Fluorine 18-fluorodeoxyglucose positron emission/computed tomography.

Table 2. Multivariate analysis associating GLA-TBR with time distance of ¹⁸F-FDG PET/CT scan from admission, adjusted for sex, age, and systematic inflammation as indicated by hs-CRP

Variables	<i>b</i> (95% CI)	SE <i>b</i>	β	<i>P</i> -value
(Dependent variable = GLA-TBR), Adjusted R² of model = 0.741				
Age	0.002 (– 0.002 to 0.007)	0.002	0.142	0.301
Sex (male vs. female)	0.070 (– 0.011 to 0.151)	0.037	0.251	0.085
hs-CRP	0.009 (0.004 to 0.015)	0.002	0.493	0.002
Days from admission to ¹⁸ F-FDG PET/CT	– 0.004 (– 0.005 to – 0.002)	0.001	– 0.576	0.001

Aortic TBR remained moderately associated with time distance from admission of COVID 19 to ¹⁸F-FDG PET/CT and with systemic inflammation assessed by hs-CRP, even after adjustment for sex and age
hs-CRP, high sensitivity C reactive protein; *TBR* target to background ratio; ¹⁸F-FDG PET/CT Fluorine 18-fluorodeoxyglucose positron emission/computed tomography

controls (GLA-TBR_{≤60 days} = 1.55 [1.47-1.61] vs. GLA-TBR_{control} = 1.43 [1.32-1.70], *P* = 0.085). However, when the same analysis was performed using IAS - TBR there was a significant difference between the two groups (IAS-TBR_{≤60 days} = 1.64 [1.51-1.74], IAS-TBR_{control} = 1.50 [1.41-1.61], *P* = 0.036) (Figure 2). Figure 3 demonstrates a patient assessed 20 days post-

admission compared to a patient assessed 64 days after admission for COVID 19.

Out of all patients, 65% (n = 13) had critical COVID 19 and required ICU admission. There was no significant difference in aortic TBR between patients admitted to ICU and patients with severe COVID disease not requiring ICU admission (global

Table 3. Multivariate analysis investigating association of IAS-TBR with time distance of ¹⁸F-FDG PET/CT scan from admission, adjusted for sex, age, and systematic inflammation as indicated by hs-CRP

Variables	<i>b</i> (95% CI)	SE <i>b</i>	β	<i>P</i> -value
(Dependent variable = IAS-TBR), Adjusted R^2 of model = 0.554				
Age	– 0.004 (– 0.007 to 0.001)	0.003	– 0.235	0.197
Sex (male vs. female)	0.068 (– 0.070 to 0.205)	0.063	0.189	0.303
hs-CRP	0.011 (0.002 to 0.020)	0.004	0.452	0.021
Days from admission to ¹⁸ F-FDG PET/CT	– 0.004 (– 0.007 to – 0.001)	0.001	– 0.494	0.014

IAS-TBR remained moderately associated with time distance from admission of COVID 19 to ¹⁸F-FDG PET/CT and with systemic inflammation assessed by hs-CRP, even after adjustment for sex and age
hs-CRP, high sensitivity C reactive protein; *TBR*, target to background ratio; ¹⁸F-FDG PET/CT, Fluorine 18-fluorodeoxyglucose positron emission/computed tomography

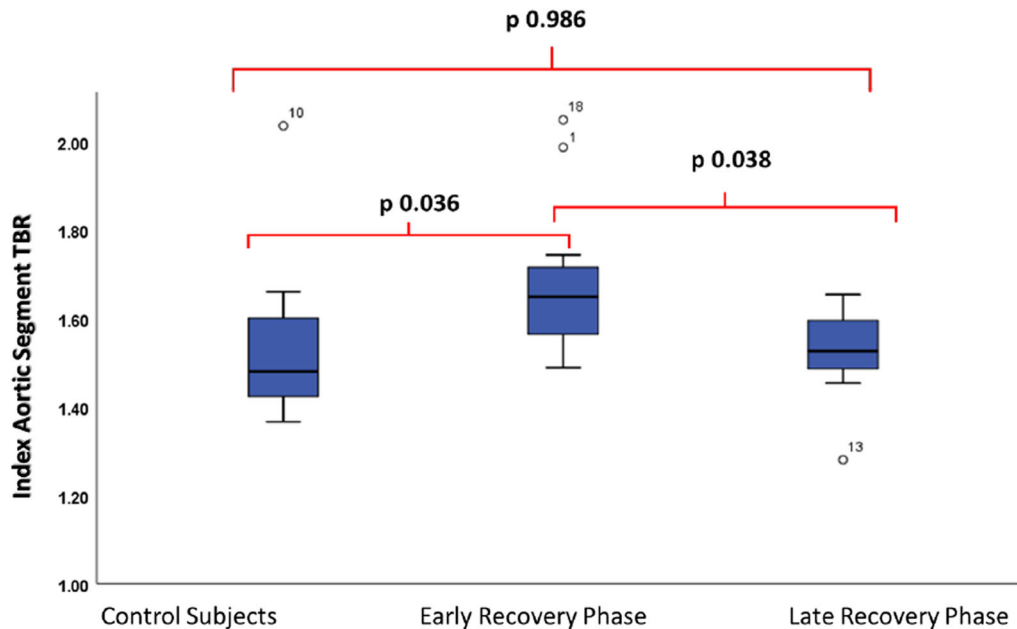


Figure 2. Boxplot demonstrating IAS-TBR in control subjects, patients scanned ≤ 60 days and > 60 days from admission for COVID 19. Significant difference in IAS-TBR between control subjects and patients scanned ≤ 60 days (Early Recovery Phase) from admission for COVID 19. On the contrary patients scanned > 60 days (Late Recovery Phase) did not demonstrate significantly different values compared to controls.

$TBR_{ICU\text{patients}} = 1.45 [1.40-1.54]$ vs global $TBR_{nonICU\text{patients}} = 1.52 [1.34-1.58]$, $P = 0.757$). Similarly, there was no significant difference in index vessel TBR in patients admitted to ICU compared to patients that were not admitted to ICU (index Vessel $TBR_{ICU\text{patients}} = 1.59 [1.49-1.67]$ vs index vessel $TBR_{nonICU\text{patients}} = 1.61 [1.52-1.69]$, $P = 0.485$).

Regarding localization of the index aortic segment in patients, higher FDG uptake values were observed more frequently in thoracic aorta ($n = 14$, 70%) compared to abdominal aorta ($n = 6$, 30%).

Regarding circulating biomarkers, there was a modest association between both global aortic TBR and index vessel TBR and CRP (Spearman's rho =

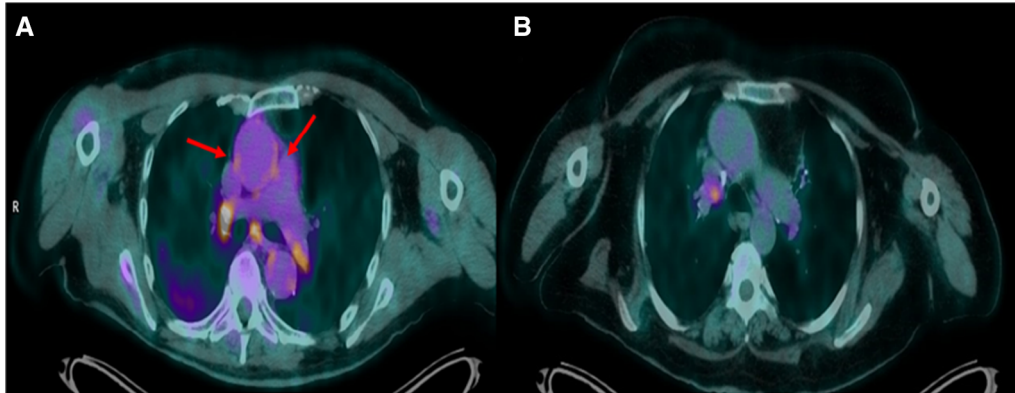


Figure 3. Transaxial views of fused ^{18}F -FDG PET/CT images of 2 patients post severe COVID 19. **A** Patient scanned twenty days post-admission of severe COVID 19. **B** Patient scanned sixty-four days after admission. In the former, there is increased ^{18}F -FDG uptake in the wall of the ascending aorta (arrows) and there are also hypermetabolic hilar and mediastinal lymph nodes. ^{18}F -FDG PET/CT: Fluorine 18-fluorodeoxyglucose positron emission/computed tomography.

Table 4. Associations of GLA-TBR/ISA-TBR and biomarkers of COVID-19 severity

	GLA-TBR		ISA-TBR	
	Spearman's rho	P-value	Spearman's rho	P-value
hs-CRP	0.662	0.004	0.559	0.020
hs-Troponin	0.044	0.871	- 0.92	0.724
D-dimers	- 0.182	0.499	0.029	0.914
Admission SO_2	0.095	0.708	0.289	0.244

hs-CRP, high sensitivity C reactive protein; TBR, target to blood ratio; GLA, global aortic; ISA, index segment aortic

0.662, $P = 0.004$ and Spearman's $\rho = 0.559$, $P = 0.020$, respectively). There was no association between neither global nor index vessel aortic FDG uptake and troponin or d-dimer levels (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study that investigates prospectively the presence of aortic inflammation during early recovery in COVID-19 in severely or critically ill patients, as assessed by aortic ^{18}F -FDG PET/CT uptake. More specifically, our findings suggest that patients scanned earlier than 60 days post COVID-19 admission, demonstrate higher aortic inflammation compared to either patients scanned later or to control subjects. The time pattern of this aortic involvement shows a largely transient involvement. Furthermore, aortic TBR values are associated with higher CRP levels during admission.

Previous knowledge

There is limited information on aortic FDG uptake in patients post COVID 19.^{11,12} Solini et al¹² showed in 10 patients that although patients and control subjects had similar vascular scores, as assessed by a semi-quantitative method, there were higher aortic TBR scores in specific aortic regions in patients (thoracic aorta, right iliac artery, femoral arteries). A retrospective analysis of ^{18}F -FDG PET/CT scans of 47 patients with long COVID-19 symptoms (persistent symptoms 4 weeks post infection), revealed that 10 patients had increased standard uptake values (SUV_{max}) mainly in the thoracic aorta.²⁰ This finding is in agreement with our hypothesis that systemic inflammation is associated with aortic inflammation and that the presence of the later could be used to identify patients with long COVID-19 syndrome and late complications after infection. Regarding the time course, our results are in keeping with indirect evidence from FDG PET/CT imaging study of Minamimoto et al²¹ who showed an

inflammatory response in mediastinal lymph nodes of patients post COVID-19, which decreased during 4 weeks of observation.

Clinical implications

Our results may have important clinical implications. ¹⁸F-FDG PET/CT is a valuable tool for assessment of inflammation in the aorta in conditions where inflammation is present, such as malignancies and hyperlipidaemia^{7,10,13} and can be used as an additional parameter for the evaluation of arterial atherosclerotic activity,²² as well as large vessel vasculitis.²³ Furthermore, it can be used in the monitoring of disease since relapse was more common in patients with vasculitis when there was high aortic ¹⁸F-FDG uptake during clinical remission.²⁴ Vascular involvement in patients with COVID-19 is common and even vaccination against SARS-CoV-2 has been associated with transient endothelial dysfunction.²⁵ Accordingly, the findings of this study could expand to identify patients at risk both the early and late post COVID-19 period. The cytokine storm induced by SARS-CoV-2 results in lung injury and multi-organ failure.²⁶ COVID-19-induced vasculitis can cause thrombosis (arterial or venous), as well as coronary or aortic dissection.¹ Histopathological post-mortem findings in COVID-19 patients have shown increased inflammatory burden in patients with a severe clinical presentation and signs of endotheliitis in various affected organs.^{2,27} Importantly, a considerable percentage of patients develop long-standing COVID-19 symptoms often in the absence of elevated traditional inflammatory markers.^{1,5,6} Interestingly, this condition is mainly associated to endothelial dysfunction²⁸ and some of these patients exhibit residual aortic inflammation,²⁰ Accordingly, assessment of aortic inflammation with ¹⁸F-FDG PET/CT could predict, or serve as a marker of, longstanding COVID-19 mandating closer follow up and offering access to potentially available treatments.

Limitations

Our study is limited by its observational nature. No individual patient serial measurements with subsequent ¹⁸F-FDG PET/CT scans were taken and this hypothesis-generating study cannot prove causality. A further limitation is the relatively small number of patients. Practical shortcomings in the COVID-19 setting due to strict staff, and patient safety protocols, necessary to prevent spreading of disease, as well as enrolment of COVID-19 patients to numerous other interventional research protocols, led to a very cumbersome and challenging recruitment process that could explain the

relatively small number of participants. Nevertheless, our study attests to the potential of this diagnostic modality to become clinically useful, when practical issues are addressed.

Our findings are provided by cross-sectional and not individual prospective data. While they overall suggest a time-related recovery of inflammation, factors of resolution and the exact time pattern still remain unknown. Further research is needed to disentangle the process of recovery of inflammation (aortic and systemic) in patients with COVID-19.

CONCLUSIONS

In conclusion, this is the first study suggesting by means of ¹⁸F-FDG PET/CT imaging that patients may demonstrate high aortic inflammation early post COVID-19; however, this aortic involvement is largely transient. ¹⁸F-FDG PET/CT imaging could recognise early patients that have residual aortic inflammation and may serve as a predictor of outcome both in the early and late post infection period. Larger prospective studies are needed to support this. In addition, our results could instigate investigation of even earlier phases of the disease.

Disclosures

There is no conflict of interest. There was no funding for this study.

Ethical approval

All procedures performed in studies 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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