# Journal Pre-proof

Persistent lung inflammation after clinical resolution of community-acquired pneumonia as measured by $^{18}$FDG-PET/CT

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# TITLE: Persistent lung inflammation after clinical resolution of community-acquired pneumonia as measured by $^{18}$FDG-PET/CT

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**Short title:** Persistent lung inflammation after pneumonia.

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## ABSTRACT

**Background:** Survivors of community-acquired pneumonia (CAP) are at increased risk of cardiovascular disease, cognitive and functional decline, and death but the mechanisms remain unknown.

**Research Question:** Do CAP survivors have evidence of increased inflammatory activity in their lung parenchyma on $^{18}$FDG-PET/CT after clinical resolution of infection?

**Study Design and Methods:** We performed $^{18}$FDG-PET/CT scans in 22 CAP-survivors during their hospitalization with pneumonia (acute-CAP) and 30-45 days after the hospital discharge (post-CAP). We assessed the lungs for foci of increased $^{18}$FDG uptake by visual interpretation and by the total pulmonary glycolytic activity (tPGA), a background-corrected measure of total metabolic activity (as measured by $^{18}$FDG uptake) of the lungs on both scans. We also measured the glycolytic activity of lung areas of volumes exactly similar to the areas of increased $^{18}$FDG uptake in the post-CAP studies of CAP participants in 28 matched historical controls without pneumonia.

**Results:** Overall, (68%, confidence interval 45% to 85%) CAP-survivors had distinct residual areas of increased $^{18}$FDG uptake in their post-CAP studies. tPGA decreased from 821.5 (standard deviation [SD], 1140.2) in the acute-CAP period to 80.0 (SD, 81.4) in the post-CAP period (p=0.006). The tPGA post CAP was significantly higher than that in lung areas of similar volume in controls (80.0 [SD, 81.4] versus -19.4 [SD, 5.9]; p<0.001).

**Interpretation:** An important proportion of CAP survivors have persistent pulmonary foci of increased inflammatory activity beyond resolution of their infection. As inflammation contributes to cardiovascular disease, cognitive decline, functional waning

and mortality risk in the general population, this finding provides a plausible mechanism for the increased morbidity and mortality that has been observed post-CAP.

**Keywords :** Pneumonia; inflammation; pneumonia-survivors; CAP-survivors

**Abbreviations :**

| | |
|---|---|
| CAP: | Community-Acquired Pneumonia |
| COPD: | Chronic Obstructive Pulmonary Disease |
| CRP: | C-reactive protein |
| CT: | Computed Tomography |
| FDG: | 18-Fluorine-2-Deoxy-D-Glucose |
| PGA: | Pneumonia Glycolytic Activity |
| PSI: | Pneumonia Severity Index |
| SD: | Standard Deviation |
| SUV: | Standardized Uptake Value |
| tPGA: | total Pulmonary Glycolytic Activity |

## INTRODUCTION

Survivors of community acquired pneumonia (CAP) remain at increased risk of cardiovascular disease, cognitive decline, functional waning and death for months after clinical resolution of their infection but the mechanisms for this increased morbidity and mortality post-CAP are unknown.[1-5] In the general population, increased inflammatory activity has been implicated in the progression of all these outcomes (cardiovascular disease, cognitive and functional decline, and death).[6] Therefore, lingering increased inflammatory activity beyond clinical resolution of CAP has been proposed as a plausible mechanism for the heightened morbidity and mortality that follows this infection.[7] However, an objective source for enduring increased inflammatory activity post-CAP has never been demonstrated. Radiographic lung infiltrates that can persist for weeks and, in some cases, months after resolution of pneumonia in a significant proportion of CAP survivors are well described but the biologic significance of this observation is unknown.[8-10] In this study, we used positron emission tomography (PET)/Computed tomography (CT) with 18-fluorine-2-deoxy-D-glucose ($^{18}$FDG-PET/CT) to investigate whether CAP survivors have persistent foci of increased inflammatory activity in their lung parenchyma after their infection has clinically resolved.

## STUDY DESIGN AND METHODS

This study was approved by the Ottawa Health Science Network Research Ethics Board (reference 20130822-01H), and all participants provided written informed consent.

We enrolled consecutive ambulatory community-dwelling adults ≥65 years-old admitted to The Ottawa Hospital (Ontario, Canada) between August, 2015 and January, 2018 who had (1) No hospitalizations in the previous 14 days; (2) At least one respiratory

symptom consistent with pneumonia (new or worsening cough, new or worsening dyspnea, new or worsening sputum production, change in the quality of baseline sputum production, or chest pain made worse with inspiration) of ≤2-week duration (to avoid inclusion of more chronic forms of pneumonia); (3) A chest radiograph with a new infiltrate consistent with pneumonia; and (4) A serum C-reactive protein (CRP) ≥15 mg/L (drawn in the first 72h of hospitalization). The latter criterion was aimed at minimizing the inclusion of cases whose clinical presentation was not secondary to an acute infectious process (i.e. COPD exacerbation or heart failure).[11-14] In addition, we excluded patients that (1) Had a baseline (pre-CAP) functional status that would make it difficult for them to return for follow-up examinations after hospital discharge; (2) Showed no clinical improvement after 48h of CAP guideline-concordant antibiotic therapy;[15] or (2) Had any known immuno-deficiency or active malignancy. The latter two criteria were aimed at minimizing the enrolment of patients at high risk of not surviving the acute CAP episode. We selected patients ≥65 years-old because this is the age-group with the highest burden of CAP[16-18] and its post-infectious complications (increased risk of cardiovascular disease, cognitive decline, functional waning and death, among others).[1-5] Thus, any demonstration of persistent lung inflammation after CAP would have the highest clinical implications in this age-group. Patients also had to be stable enough to be transported to the $^{18}$FDG/PET/CT suite safely and endure the technical requirements of this test. As a result, patients that were hemodynamically unstable, requiring vasopressors, or needing high O2 supplements or mechanical ventilation were not included.

We performed serial $^{18}$FDG-PET/CT imaging using a Discovery 690 scanner (GE Healthcare, Waukesha, WI) at 48h-96h after participants' hospitalization ("acute-CAP" studies) and at 30-45 days after their hospital discharge ("post-CAP" studies).

$^{18}$FDG-PET/CT is used for the measurement of inflammation in the current study. In the absence of other causes of increased metabolic activity including benign and malignant lesions or an active infectious process, uptake of $^{18}$FDG (a radio-labelled glucose analogue) in lungs reflects increased inflammatory activity because of the higher metabolic rate of inflammatory cells compared to vascular and parenchymal cells.[8]

PET/CT studies were analyzed by level-3 qualified experts. A first assessment included the visual characterization of patterns of $^{18}$FDG uptake in the lung parenchyma of CAP-survivors from the acute to the post-CAP states (i.e. resolution, improvement but still with distinct areas of increased $^{18}$FDG uptake, and overall unchanged or worsening). A background-corrected measure of total metabolic activity (similar to the total lesion glycolysis used in cancer patients), the total pulmonary glycolytic activity (**tPGA**) was calculated on $^{18}$FDG-PET/CT studies.[19,20] A case of CAP of the right middle lung lobe in shown in **Figure 1**. In short, we used the semi-automated program HERMES Hybrid Viewer™ (Stockholm, Sweden) to define, from the co-registered images of the PET and CT scans, the entire three-dimensional volume of each lung (right and left). Each lung volume was then divided, when appropriate, into 2 separate sub-volumes: (1) the distinct areas of increased $^{18}$FDG uptake that corresponded with lung infiltrates on CT imaging ($VOL_{PNA}$), and (2) the complementary lung with otherwise unremarkable (i.e. "background") $^{18}$FDG uptake ($VOL_{BKG}$). The mean $^{18}$FDG standardized uptake value

(SUV) was measured in each sub-volume ($SUV_{PNA}$ and $SUV_{BKG}$). The pneumonia glycolytic activity (PGA) of each lung was then estimated as follows:$PGA = VOL_{PNA} \times (SUV_{PNA} - SUV_{BKG})$

Depending on whether there were areas of pneumonia in only one or both lugs, the tPGA for each $^{18}$FDG-PET/CT study was estimated by adding the PGAs of each lung (right and left) in the said study. Post-CAP $^{18}$FDG-PET/CT studies in which no apparent distinct area of increased $^{18}$FDG uptake was identified were arbitrarily assigned a volume of 0 and accordingly, a tPGA value of also 0.

We prospectively calculated the Pneumonia Severity Index (PSI) score for each patient at the time of their hospital presentation.[21] We measured CRP serum levels within the first 72h of hospitalization (24h to 48h before the first $^{18}$FDG-PET/CT study) and on the same day of the post-CAP $^{18}$FDG-PET/CT studies.

We also identified historical controls matched to CAP-patients by age and sex. These controls had clinically indicated $^{18}$FDG-PET/CT studies for evaluation of possible malignancy but benign final diagnoses. Based on the average $VOL_{PNA}$ volumes from the post-CAP patient studies, spheres of half this volume were drawn at random central locations in both lungs of each historical control. These spheres were treated the same way as the 'pneumonia' areas in CAP-survivors and their glycolytic activity was computed using the same method as described above. We did this to estimate the expected glycolytic activity of lung areas with volumes similar to the areas with increased $^{18}$FDG uptake in the post-CAP studies of CAP participants but in patients that do not have history of this infection.

About two-thirds of elderly CAP survivors exhibit persistent pneumonia-associated radiographic infiltrates after CAP clinical resolution .[10] [18]FDG-PET/CT is a more sensitive technique for lung parenchymal abnormalities than x-rays. Our study was powered to detect a 65% prevalence of persistent inflammatory foci in lung parenchyma of elderly CAP survivors with a margin of error of 20% and a confidence level of 95%.

Using descriptive, chi-square and t-test (paired and independent-sample) statistics, as appropriate, we compared baseline characteristics of CAP-patients versus controls, and CAP-patients' tPGA and CRP serum levels in the acute-CAP versus post-CAP states. For comparisons between the post-CAP tPGA of CAP patients versus the lung volume-matched glycolytic activity of controls, we used simple linear regression with the post-CAP tPGA values (for CAP patients) or the lung volume-matched glycolytic activity values (for controls) as the outcome, pneumonia vs. control as the exposure, and any baseline characteristic that differed between groups (with a *P* significance level of <0.2) as covariate(s). We also explored correlations between CRP and PSI values with tPGA using the Pearson coefficient of correlation. Kappa statistics was used to measure the concordance between tPGA values and visual interpretation of scans. A two-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed using the Matlab statistics and machine learning toolbox (Matlab 2016b, the Mathworks; Natwick, MA).

## RESULTS

### Participant Characteristics

A flow diagram of the recruitment process in our study is presented in **e-Figure 1**. We initially enrolled 28 patients in the acute phase of CAP. However, 6 declined to return for their post-CAP examinations and were subsequently excluded. As a result, 22 patients with completed acute and post-CAP examinations are included in this report. We also identified 28 matched historical controls. The baseline clinical characteristics of the pneumonia participants and controls are presented in **Table 1**.

**Patterns of progression of $^{18}$FDG uptake after clinical resolution of CAP**

Representative patterns of $^{18}$FDG uptake in lung parenchyma from the acute- to the post-CAP studies are presented in **Figure 2**. Overall, 15 (68.2%, confidence interval 45.1% to 85.2%) of CAP-survivors still showed distinct areas of increased $^{18}$FDG uptake (improved, unchanged or worsened from previous) in their post-CAP studies.

**tPGA during and after CAP and comparison with controls**

Strong agreement (kappa=0.80) was found between the expert reader's visual interpretation of direction and magnitude of change of FDG uptake from acute to post-pneumonia scan and the difference in tPGA values between the two scans. The progression of tPGA from the acute- to the post-CAP in each CAP patient is depicted in **e-Figure 2**. tPGA decreased significantly from 821.5 (standard deviation [SD], 1140.2) to 80.0 (SD, 81.4) in the acute- and post-CAP periods, respectively (p=0.006). However, post-CAP tPGA values in CAP-survivors were still significantly higher than zero (p<0.001), and also higher than glycolytic activity values of volume matched lung areas in controls (80.0 [SD, 81.4] versus -19.4 [SD, 5.9]; adjusted p<0.001) (**Figure 3**).

**Associations of PSI and CRP with tPGA**

PSI score values did not correlate with acute- or post-CAP tPGA values ($r^2$, 0.007; p=0.701; and $r^2$, 0.002; p=0.817, respectively). Serum CRP values decreased significantly from the acute-CAP to the post-CAP periods (112.5 [SD, 60.2] mg/L vs. 7.8 [SD, 12.3] mg/L, respectively; p <0.001). Acute-CAP CRP levels correlated directly with acute-CAP tPGA values ($r^2$=0.34; p=0.002) but not with post-CAP tPGA values ($r^2$=0.0009; p=0.893). Post-CAP CRP values did not correlate with acute- or post-CAP tPGA values ($r^2$, 0.003; p=0.800; and $r^2$, 0.0002; p=0.940, respectively). The difference in CRP levels between acute-CAP and post-CAP values correlated with the difference in tPGA between acute-CAP and post-CAP values ($r^2$, 0.39; p=0.002).

**DISCUSSION**

To the best of our knowledge, this is the first series of CAP survivors investigated with $^{18}$FDG PET/CT. Herein, we demonstrated that a significant proportion of CAP survivors (68.2% in our study) continue having distinct foci of increased inflammatory activity in their lung parenchyma for several weeks after the clinical resolution of their infection. While persistent radiographic lung parenchymal infiltrates after clinical resolution of pneumonia are well described among CAP survivors,[8,9] we are not aware of any previous report (in humans or otherwise) documenting residual biologically active parenchymal abnormalities in the lungs of such patients.

Increased uptake of $^{18}$FDG (a glucose analogue) denotes increased cellular metabolic activity. In tissues of mostly uniform cellular metabolic activity with no

meaningful glucose storage capacity such as the lung parenchyma,[22] focal increased $^{18}$FDG uptake in PET images reflects malignancy or infectious/inflammatory activity.[23] In our population of CAP survivors, their initial syndromic presentation consistent with pneumonia, their acutely elevated CRP levels, their clinical response to pneumonia-directed therapy, and the dynamic change of $^{18}$FDG uptake over time make it all but certain that the residual areas of focal increased $^{18}$FDG uptake seen in their lung parenchyma in the post-CAP studies represent residual foci of inflammatory activity related to the -by then treated- index infection. However, the clinical significance of this finding and the nature of the local inflammatory cells and humoral mediators that contribute to this residual inflammation remain unknown.

Our estimation of tPGA is similar to the estimation of total lesion glycolysis for lung cancer lesions.[19,20] In our study, tPGA is a background-corrected measure of the total metabolic activity (as measured by $^{18}$FDG uptake) of lung areas seemingly affected by pneumonia. tPGA allowed us to estimate not only the magnitude of decrease in metabolic activity associated with -presumed- pneumonia lesions from the acute-CAP to the post-CAP periods but also the magnitude of the residual increased pneumonia-associated metabolic activity in affected lung areas in CAP-survivors relative to volume-matched lung areas in controls without recent pneumonia (about 4-fold higher in our study). Currently however, we can make no inference about the clinical significance of these differences.

The lack of association between PSI and tPGA (both at the acute-CAP and post-CAP periods) is not unexpected. While tPGA is an approximation of the total metabolic activity associated with discrete pneumonia lesions, PSI is a validated 20-item (3

demographic criteria, 5 pre-existing co-morbidities, 5 physical-examination findings, and 7 selected laboratory and radiographic findings) score built to predict 30-day mortality of patients presenting with CAP to an emergency department.[21] Thus, any putative association of tPGA with clinical outcomes (short or longer-term) will require confirmation with dedicated investigations.

Serum CRP is an acute phase reactant that is widely used as unspecific marker of inflammation.[24] Serum CRP elevations have been broadly associated with the activity of infections and inflammatory rheumatological conditions.[25,26] In response to an acute inflammatory insult, CRP levels peak in the early phase of the inflammatory response.[24] Predictably, serum CRP values correlated with tPGA at the acute-CAP period. However, at the post-CAP period, not such association was demonstrated. Inflammation is one of the most dynamic and multifaceted biological processes with a variety of triggers, cellular and humoral actors, and regulatory pathways.[24,27] CRP, therefore, may not be a suitable biomarker for the post-infectious inflammatory activity in lung parenchyma demonstrated our study and dedicated investigations will be needed to identify more accurate biomarkers of this occurrence. Such investigations, along with the development of animal models of this observation should assist in the elucidation of the biological processes governing this phenomenon.

Radiographic lung infiltrates that outlive the clinical resolution of CAP have been well described.[8,9] It intuitively follows that such residual radiographic abnormalities post-CAP should correspond to the areas of persistent inflammatory activity demonstrated in our study. However, the validity and strength of such association will also need to be tested in dedicated studies.

Inflammatory activity is associated with the progression of cardiovascular disease, cognitive and functional decline, and mortality risk in the general population.[6] The risk of these outcomes also increases after CAP and remains elevated for months after resolution of the infection.[1-5] Our novel finding of lingering foci of inflammatory activity in the lung parenchyma of CAP-survivors provides a plausible mechanism for this increased morbidity and mortality post-CAP and its contribution to this phenomenon needs to be further investigated in experimental and clinical studies. [1-5] Such investigations, along with the elucidation of the biological pathways driving post-CAP lung inflammation, could then inform therapeutic interventions targeting this phenomenon to improve post-CAP outcomes. This is especially relevant to post-CAP cardiovascular risk since directed anti-inflammatory interventions have already proven beneficial in other (non-CAP) high-cardiovascular-risk groups.[28,29]

Our study is limited by its relatively small sample size. In addition, we were unable to determine the full duration of increased lung FDG uptake, as we did not perform further $^{18}$F-FDG beyond the 4-6 weeks post-CAP. Because of our sample size, we could not explore associations with incident adverse clinical events known to be associated with CAP in the medium- and long-term.[1-5] We only enrolled patients aged >65 years who were clinically stable enough to endure the technical requirements for the performance of a $^{18}$FDG-PET/CT scan in the acute phase of CAP, and had a baseline (pre-CAP) functional level that would make it likely for them to return for their convalescent examinations. Therefore, it is unknown whether our observations apply to younger age-groups, individuals with worse systemic compromise from CAP or worse baseline functional status. We used the PSI as a surrogate for severity of CAP, as

previously reported.[21] However, PSI is highly age-dependent and it has been suggested that other tools like the IDSA/ATS criteria for severe CAP are better measures of disease severity.[30] Unfortunately, we did not evaluate those other tools. As the serum CRP measurements used for inclusion in our study (i.e. CRP ≥15 mg/L) were not drawn at the time of patients' presentation to hospital but within 72h of hospital admission, it is possible that we selected for patients prone to more prolonged inflammatory responses (as opposed to patients with tendency to resolve their acute inflammatory responses quickly). Finally, while we assessed associations between lung FDG uptake and CRP, we did not evaluate other more specific inflammatory pathways that could be linked to persistent lung inflammation after CAP.

## INTERPRETATION

In conclusion, an important proportion of CAP-survivors demonstrate persistently increased inflammatory activity in their lung parenchyma well beyond clinical resolution of their infection. This novel finding provides a plausible mechanism that might contribute to the adverse morbidity and mortality that follows CAP.

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**TAKE HOME POINTS**

**Question:** We investigated if community-acquired pneumonia (CAP) survivors have evidence of increased inflammatory activity in their lung parenchyma on $^{18}$FDG-PET/CT after clinical resolution of infection?

**Results:** In this study of 22 CAP-survivors and 28 controls, 68% of CAP-survivors had distinct residual areas of increased $^{18}$FDG uptake in their post-CAP scans. Furthermore, the post-CAP scans of the pneumonia survivors showed a significantly higher inflammatory activity compared to controls.

**Interpretation:** Persistent pulmonary foci of increased inflammatory activity beyond clinical resolution of the infection may provide a plausible mechanism for the increased morbidity and mortality observed post-CAP.

**Table 1 title:** Clinical characteristics of patients with community-acquired pneumonia (CAP) and controls

**Table 1 legend:** SD denotes standard deviation. PSI denotes pneumonia severity index. NA denotes not applicable.

**Figure 1 title:** Estimation of the total pulmonary glycolytic activity (tPGA) in a patient with community-acquired pneumonia of the right middle lung lobe

**Figure 1 legend:** Using the semi-automated program HERMES Hybrid Viewer™ (Stockholm, Sweden) and the co-registered images PET and CT of the $^{18}$FDG-PET/CT , the entire three-dimensional volumes of each lung (right and left) are defined. Each lung volume is then divided, when appropriate, into 2 separate sub-volumes: (1) the distinct areas of increased $^{18}$FDG uptake corresponding to lung infiltrates on CT imaging ($VOL_{PNA}$), and (2) the complementary lung with otherwise unremarkable (i.e "background") $^{18}$FDG uptake ($VOL_{BKG}$). The mean $^{18}$FDG standardized uptake value (SUV) is then measured in each sub-volume ($SUV_{pneumonia}$ and $SUV_{background}$). The pneumonia glycolytic activity (PGA) of each lung is then estimated as follows:

$$PGA = VOL_{PNA} \times \left(SUV_{PNA} - SUV_{BKG}\right)$$

the **tPGA** for the whole study is estimated by adding the PGAs of each lung (right and left). In this case, as there was no obvious infiltrate in the left lung, the tPGA value will be equal to the PGA value for the right lung.

**Figure 2 title:** Visual patterns of progression of $^{18}$FDG uptake in the lung parenchyma of 22 survivors of community-acquired pneumonia (CAP)

**Figure 2 legend:** $^{18}$FDG denotes 18-fluorine-2-deoxy-D-glucose**.** Added circles enclose discrete areas of lung parenchyma with increased $^{18}$FDG uptake.

**Figure 3 title:** Glycolytic activity of lung areas affected by pneumonia in survivors of community-acquired pneumonia (CAP) and in volume-matched lung areas of controls.

**Figure 3 legend:** Acute-CAP denotes measurement during hospitalization for CAP. Post CAP denotes measurements at 3040-34 45 days after hospital discharge. tPGA denotes total pulmonary glycolytic activity. The p value for the comparison between post-CAP measurements and the measurements in controls is adjusted for the difference in the prevalence of heart failure, stroke, hypertension and dyslipidemia between the groups (see Table 1).

**e-Figure 1 title:** Flow diagram of the study recruitment process

**e-Figure 1 legend:** CAP denotes community-acquired pneumonia. $^{18}$FDG-PET/CT denotes positron emission tomography (PET)/Computed tomography (CT) with 18-fluorine-2-deoxy-D-glucose

**e-Figure 2 title:** Total pulmonary glycolytic activity (tPGA) in patients

**e-Figure 2 legend:** Progression of the total pulmonary glycolytic activity (tPGA) in patients with community-acquired pneumonia (CAP) from the acute stage (acute CAP, 48h-96h after hospitalization for CAP) to the convalescent stage (30-45 days after hospital discharge)

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VFCM and GD led the project and are responsible for all content in the manuscript. All authors approved the analysis plan. RAD, WZ and JW performed the analyses. VFCM and GD drafted the manuscript. All authors contributed to interpretation of the results and revision of the manuscript for important intellectual content, and approved its submission.

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**Figure 1.**

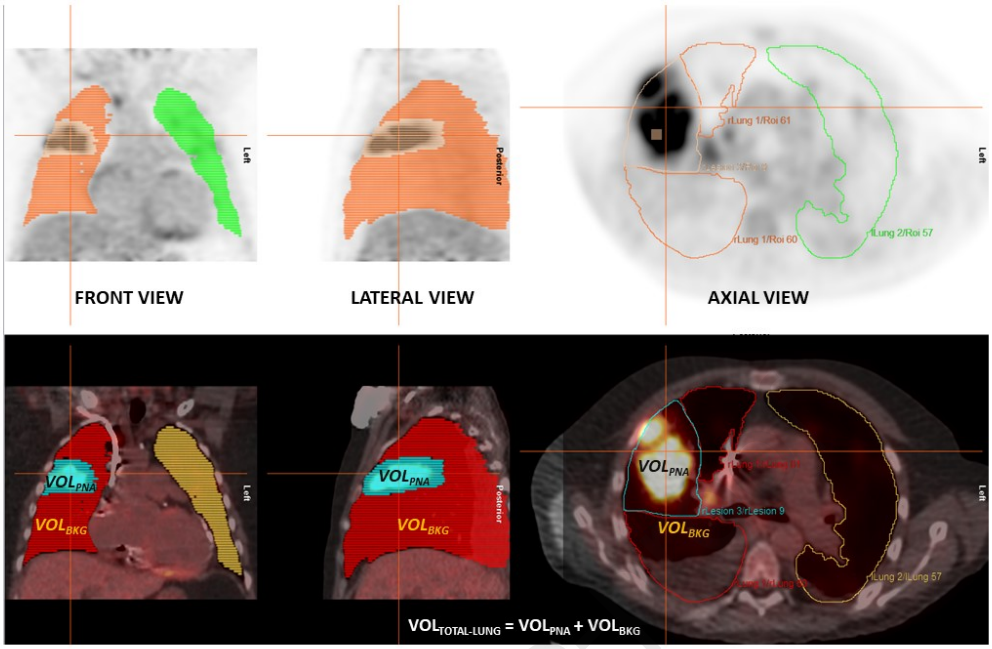

**Figure 2.**

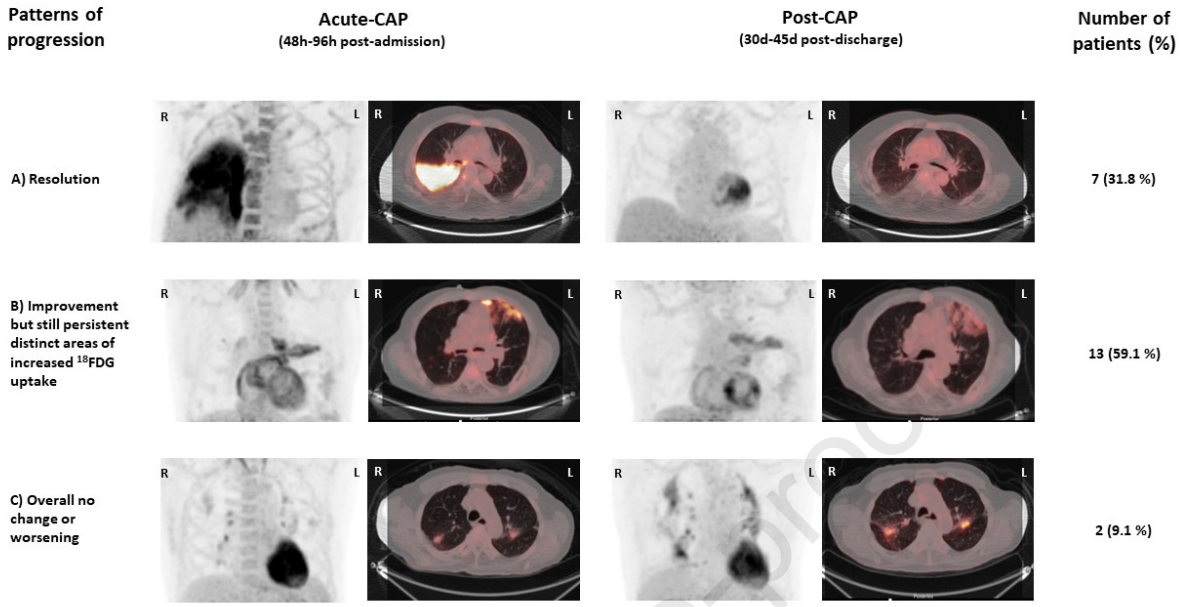

**Figure 3.**

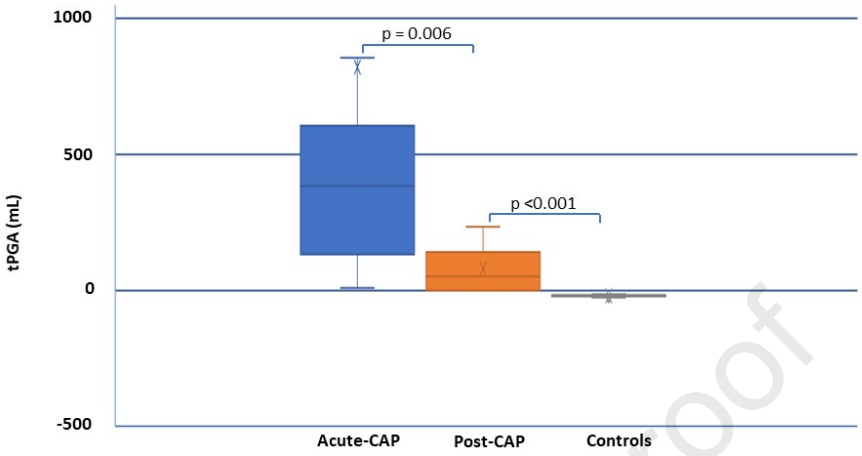

**Table 1.**

| **Baseline characteristics** | **CAP cases n = 22** | **Controls n = 22** | **P-value** |
|---|---|---|---|
| Mean age ± SD | 79 ± 9 | 77 ± 8 | 0.552 |
| Male sex (%) | 11 (50%) | 15 (54%) | 0.802 |
| History of: | | | |
| Heart failure (%) | 7 (32%) | 1 (4%) | 0.023 |
| Coronary artery disease (%) | 6 (27%) | 7 (25%) | 0.856 |
| Stroke (%) | 0 (0%) | 6 (21%) | 0.028 |
| Hypertension (%) | 7 (32%) | 16 (57%) | 0.074 |
| Dyslipidemia (%) | 9 (41%) | 17 (61%) | 0.164 |
| Smoking (%) | 8 (36%) | 7 (25%) | 0.384 |
| Chronic obstructive pulmonary disease (%) | 8 (36%) | 8 (29%) | 0.558 |
| Diabetes (%) | 6 (27%) | 4 (14%) | 0.254 |
| End-stage renal disease (%) | 0 (0%) | 0 (0%) | NA |
| Mean PSI score ± SD | 97 ± 26 | NA | NA |
| Mean length of hospital stay ± SD | 4 ± 1 | NA | NA |