Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Epicardial adipose tissue is associated with extent of pneumonia and adverse outcomes in patients with COVID-19

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ABSTRACT

Aim: We sought to examine the association of epicardial adipose tissue (EAT) quantified on chest computed tomography (CT) with the extent of pneumonia and adverse outcomes in patients with coronavirus disease 2019 (COVID-19).

Methods: We performed a post-hoc analysis of a prospective international registry comprising 109 consecutive patients (age 64 ± 16 years; 62% male) with laboratory-confirmed COVID-19 and noncontrast chest CT imaging. Using semi-automated software, we quantified the burden (%) of lung abnormalities associated with COVID-19 pneumonia. EAT volume (mL) and attenuation (Hounsfield units) were measured using deep learning software. The primary outcome was clinical deterioration (intensive care unit admission, invasive mechanical ventilation, or vasopressor therapy) or in-hospital death.

Results: In multivariable linear regression analysis adjusted for patient comorbidities, the total burden of COVID-19 pneumonia was associated with EAT volume ($\beta = 10.6$, $p = 0.005$) and EAT attenuation ($\beta = 5.2$, $p = 0.004$). EAT volume correlated with serum levels of lactate dehydrogenase ($r = 0.361$, $p = 0.001$) and C-reactive protein ($r = 0.450$, $p < 0.001$). Clinical deterioration or death occurred in 23 (21.1%) patients at a median of 3 days (IQR 1–13 days) following the chest CT. In multivariable logistic regression analysis, EAT volume (OR 5.1 [95% CI 1.8–14.1] per doubling $p = 0.011$) and EAT attenuation (OR 3.4 [95% CI 1.5–7.5] per 5 Hounsfield unit increase, $p = 0.003$) were independent predictors of clinical deterioration or death, as was total pneumonia burden (OR 2.5, 95% CI 1.4–4.6, $p = 0.002$), chronic lung disease (OR 1.3 [95% CI 1.1–1.7], $p = 0.011$), and history of heart failure (OR 3.5 [95% 1.1–8.2], $p = 0.037$).

Conclusions: EAT measures quantified from chest CT are independently associated with extent of pneumonia and adverse outcomes in patients with COVID-19, lending support to their use in clinical risk stratification.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic and public health crisis of catastrophic proportions, with over 40 million confirmed cases worldwide as of October 20th 2020 [1]. Although the majority of patients present with no or mild symptoms, up to 20% develop severe disease requiring hospitalization, with 5–8% subsequently being admitted to the intensive care unit (ICU) [2]. Chest computed tomography (CT) is highly sensitive for the diagnosis of COVID-19 pneumonia [3], and the extent of lung abnormalities reflects the disease

Abbreviations: ACE-2, angiotensin-converting enzyme 2; BMI, body mass index; COVID-19, Coronavirus disease 2019; CRP, c-reactive protein; CT, computed tomography; ICU, intensive care unit; EAT, epicardial adipose tissue; GGO, ground glass opacities; HU, Hounsfield unit; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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stage [4–6]. Obesity has been shown to associate with critical illness, need for ICU admission, and prolonged hospitalization in patients with COVID-19 pneumonia [2,7–12], however the underlying pathophysiologic mechanisms remain unclear [13]. Epicardial adipose tissue (EAT) is an active endocrine organ which modulates the metabolic environment of both the coronary arteries and myocardium [14]. EAT volume measured on CT has been shown to associate with lung function in both healthy individuals and those with chronic lung disease [15–18]. Further, CT-derived EAT attenuation (Hounsfield Units [HU]) has an established association with cardiometabolic risk factors and circulating inflammatory markers [19,20]. COVID-19 induces an immune-mediated systemic inflammatory response [21] and it has been postulated that EAT may transduce this inflammation to the heart [22,23]. Moreover, ectopic intrapulmonary fat reservoirs could potentially facilitate viral infiltration and promote local lung inflammation [24,25]. Few studies have evaluated the relationship of EAT measures with radiological and clinical severity of COVID-19 pneumonia [26,27]. In this post-hoc analysis of a prospective, international, multicenter registry, we sought to examine the association of CT-derived quantitative EAT volume and attenuation with pneumonia burden and adverse outcomes in hospitalized patients with COVID-19.

2. Materials and methods

2.1. Study design

This prospective, international, multicenter registry included centers from North America (Cedars Sinai Medical Center, Los Angeles, USA [n = 17]) and Europe (Centro Cardiologico Monzino [n = 75], and Istituto Auxologico Italiano [n = 17]; both Milan, Italy). Consecutive patients who underwent noncontrast chest CT and had a positive reverse transcription polymerase chain reaction (RT-PCR) test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during index admission between January 10 and April 14, 2020 (Fig. 1) were enrolled. Chest CT was performed to aid in the triage of patients with a high clinical suspicion for COVID-19, in the setting of a pending or negative RT-PCR or comorbidities associated with severe illness from COVID-19. The CT images from each patient and the clinical database were fully anonymized and transferred to one coordinating center for core lab analysis. The study was conducted with the approval of local institutional review boards (Cedars-Sinai Medical Center IRB# study 617) and written informed consent was waived for fully anonymized data analysis.

2.2. Scan protocol and image reconstruction

Noncontrast chest CT scans were performed with different multi-slice CT systems: Aquilion ONE (Toshiba Medical Systems, Otawara, Japan); GE Revolution, GE Discovery CT750 HD, or LightSpeed VCT (GE Healthcare, Milwaukee, WI, USA); and Brilliance iCT (Philips Healthcare, Cleveland, OH, USA). Parameters used for scans included a peak x-ray tube voltage of 120 kV, automatic tube current modulation (300–500 mAs), and slice thickness of 0.625 to 1.25 mm. Images were reconstructed using lung kernels specific for respective scanner vendors. All scans were obtained in the supine position during inspiratory breath-hold.

2.3. CT lung analysis

Images were analyzed by two physicians (K.G. and A.L.) with 3 and 8 years of experience in chest CT, respectively, and who were blinded to clinical data. A standard lung window (width: 1500 Hounsfield units [HU]; level: −400 HU) was used. Lung abnormalities were quantified using semi-automated research software (FusionQuant Lung v1.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA). First, both lungs were segmented by a deep learning model based on U-Net architecture [28]. The acquired pulmonary mask and a second deep learning model trained with the Lung Tissue Research Consortium dataset were then used to compute lobe segmentations, with manual adjustments made by the reader as required [29]. The right lung was divided into upper, middle, and lower lobes with respect to the horizontal and oblique fissures; while the left lung was separated into upper and lower lobes by the oblique fissure.

Lung lesions associated with COVID-19 pneumonia were then segmented using a semi-automated brush-like tool; the boundaries of which were delimited by a region-growing algorithm. These included ground glass opacities (GGO), consolidation, or pleural effusion according to the Fleischner Society lexicon (Fig. 2A–B) [30,31]. Adaptive thresholds were used, defined by a fixed window around the HU of the selected voxel. Chronic lung abnormalities such as emphysema or fibrosis were excluded from segmentation, based on correlation with previous imaging and/or a consensus reading. GGO was defined as hazy opacities that did not obscure the underlying bronchial structures or pulmonary vessels; consolidation as opacification obscuring the

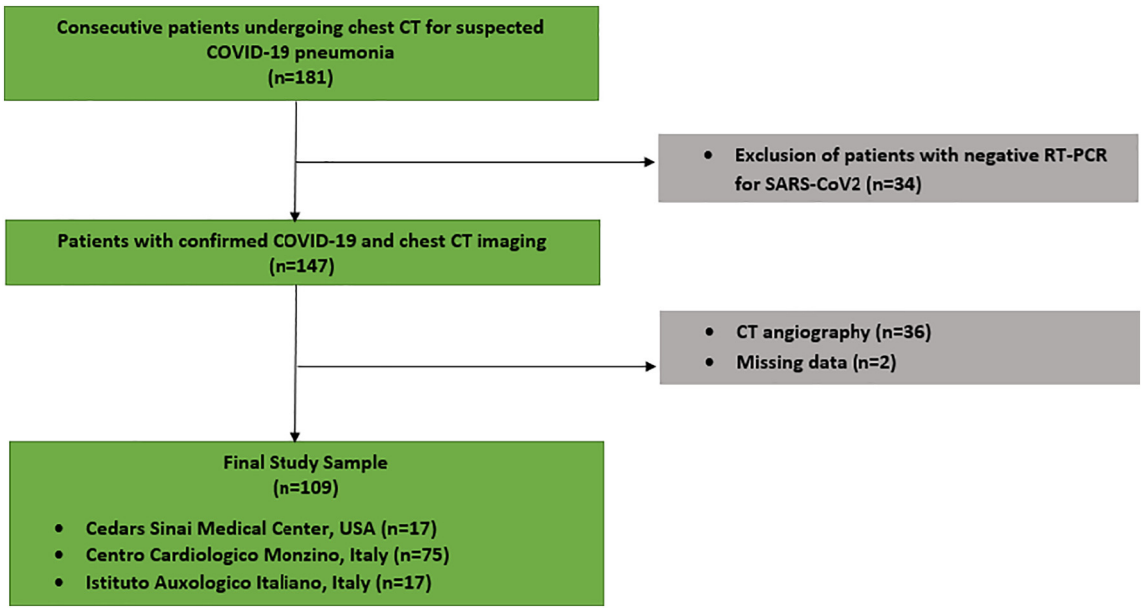

Fig. 1. Study flowchart.

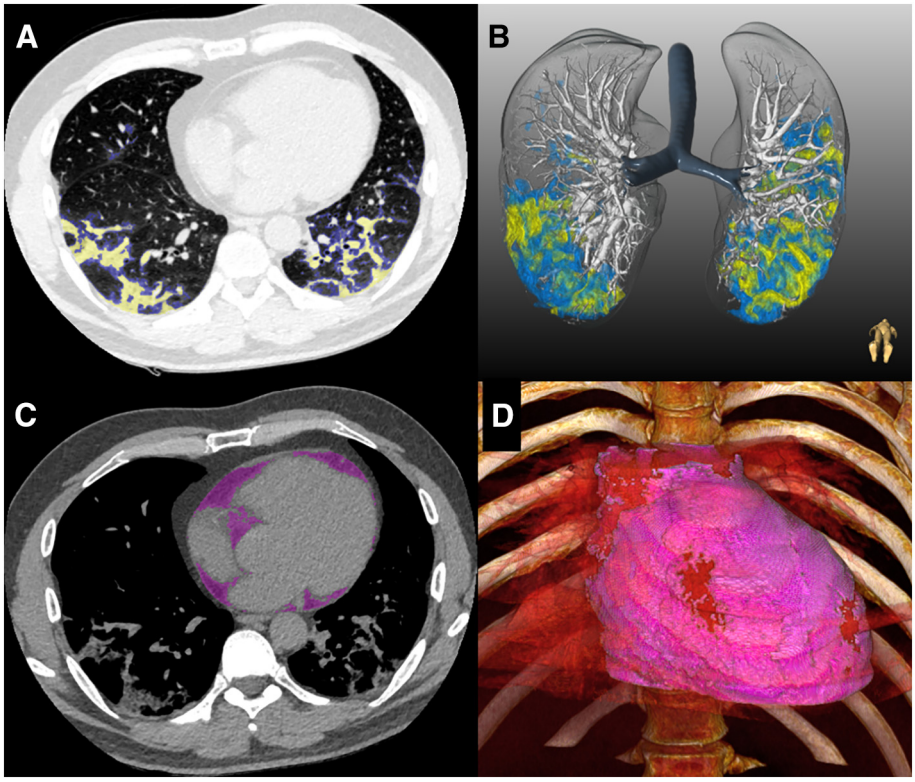

Fig. 2. Quantitative CT analysis in COVID-19 patient. Semi-automated segmentation of ground-glass opacities (blue) and consolidation (yellow) was performed using axial slices (A) and reconstructed in 3D (B). Epicardial adipose tissue (purple) was segmented using a deep learning algorithm (C) and volume-rendered (D).

underlying bronchial structures or pulmonary vessels; and pleural effusion as a fluid collection in the pleural cavity. Total pneumonia volume was calculated by summing the volumes of the GGO and consolidation components. Total pneumonia burden was calculated as: total pneumonia volume / total lung volume × 100% [31].

The average time taken for full lung and lesion segmentation ranged from 10 to 20 min depending on patient anatomy and the extent of pneumonia. The axial distribution of lung abnormalities was visually classified as peripheral (predominantly outer one-third of the lung), central (predominantly inner two-thirds of the lung), or diffuse (no clear distribution pattern [6]. Difficult cases of visual or quantitative analysis were resolved by consensus. The presence of any breathing artifact was also noted.

2.4. EAT quantification from chest CT

EAT was defined as all adipose tissue enclosed by the visceral pericardium [32,33]. EAT volume and attenuation were quantified using a deep learning algorithm incorporated into research software (QFAT version 2.0; Cedars-Sinai Medical Center). The development and validation of this automated method have been described previously [32,33]. Briefly, the limits of the heart were automatically defined as the pulmonary artery bifurcation (superior limit) to the posterior descending artery (inferior limit) and pericardial contours traced by the algorithm. For ungated CT data in our cohort, the pericardial contours were adjusted if needed. EAT volume (reported in mL) and mean attenuation (reported in HU) were automatically calculated from 3-dimensional fat voxels between the HU limits of −190 and −30 HU (Fig. 2C–D).

2.5. Outcomes and definitions

The primary outcome was a composite of clinical deterioration (intensive care unit [ICU] admission, invasive mechanical ventilation, or vasopressor therapy) or death. The time to the first occurrence of any one of the components was documented. Chronic lung disease included asthma, chronic obstructive pulmonary disease, and/or obstructive sleep apnea. Chronic kidney disease was defined as eGFR <60 mL/min/1.73m^2. Immunodeficiency was defined as active cancer treated with chemotherapy or human immunodeficiency virus infection. Patient symptoms were self-reported upon hospital admission. Serum levels of biomarkers were obtained at hospital admission.

2.6. Statistical analysis

Data were tested for normality using the Shapiro–Wilk test. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as absolute numbers (percentage). Continuous variables were compared using the Student's *t*-test or nonparametric Mann-Whitney *U* test, as appropriate. Categorical variables were compared using a Chi-square test. Correlations between continuous variables were assessed using the Spearman's rank correlation coefficient. We performed multivariate linear regression to examine the association of EAT measures with total pneumonia burden, adjusted for age, sex, and comorbidities previously shown to associate with severe illness from COVID-19 (diabetes mellitus, hypertension, smoking, chronic lung disease, history of coronary artery disease, and history of heart failure) [34,35]. To evaluate the predictive value of EAT measures for the primary outcome, we performed multivariable logistic regression analysis, adjusted for total pneumonia burden and the above clinical parameters. Quantitative pneumonia burden and EAT volume were not normally distributed and hence normalized with logarithmic adjustment; base-2 log transformation was used as this represented doubling of the variable. We selected the optimum cutoffs for EAT volume by identifying the ROC values that maximized Youden's J statistic (sensitivity + specificity - 1). A 2-sided p-value <0.05 was considered statistically significant. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient characteristics

A total of 109 patients (age 64 ± 16 years; 62% male) with laboratory-confirmed COVID-19 who underwent chest CT during their admission were included. The primary outcome occurred in 23 (21.1%) patients: 15 (65.2%) were admitted to ICU, 10 (43.5%) required mechanical ventilation, 10 (43.5%) required vasopressors, and 13 (56.5%) had in-hospital death. The median time from self-reported onset of symptoms to chest CT was 7 days (IQR 5–9 days), and the median time from chest CT to the occurrence of the primary outcome was 3 days (IQR 1–13 days). The remaining patients (n = 86; 78.9%) did not require critical care or had been discharged alive at the time of data collection. Patients who experienced deterioration or died were older and had a greater number of comorbidities (Table 1). No significant differences in body mass index (BMI) were observed between the two groups (p = 0.526). Serum inflammatory markers were increased in patients with versus without the primary outcome (Table 1).

Table 1
Clinical and laboratory characteristics of patients on admission.

	Clinical deterioration or death		P value
	Yes (N = 23)	No (N = 86)	
Clinical characteristics			
Age, years	74 ± 11	61 ± 16	<0.001
Male sex	16	52	0.424
Body mass index, kg/m^2	26.9 ± 5.1, 12	26.1 ± 3.7, 68	0.526
Hypertension	18 (78.3)	40 (46.5)	0.007
Diabetes mellitus	12 (52.2)	11 (12.8)	<0.001
Hyperlipidemia	14 (60.9)	23 (26.7)	0.002
Smoking status			0.463
Former smoker	4 (17.4)	10 (11.6)	
Current smoker	0	4 (4.7)	
History of lung disease	6 (26.1)	9 (10.5)	0.053
History of heart failure	9 (39.1)	7 (8.1)	<0.001
History of coronary artery disease	10 (43.5)	15 (17.4)	0.008
Chronic kidney disease	9 (39.1)	5 (5.8)	<0.001
Immunodeficiency	2 (8.7)	1 (1.2)	0.050
Symptoms			
Fever	13 (56.5)	66 (76.7)	0.054
Chills	1 (4.3)	7 (8.1)	0.536
Fatigue	16 (69.6)	63 (73.3)	0.724
Dyspnea	17 (73.9)	47 (54.7)	0.096
Dry cough	14 (60.9)	40 (45.5)	0.221
Sputum production	0	5 (5.8)	0.236
Hemoptysis	0	1 (1.2)	0.603
Sore throat	0	1 (1.2)	0.603
Loss of smell	0	7 (8.1)	0.157
Loss of taste	0	5 (5.8)	0.236
Muscle/joint pain	11 (47.8)	43 (50.0)	0.853
Headache	6 (26.1)	20 (23.3)	0.777
Nasal congestion	3 (13.0)	6 (7.0)	0.347
Nausea or vomiting	3 (13.0)	6 (7.0)	0.348
Diarrhea	1 (4.3)	9 (10.5)	0.367
Blood biomarkers			
Lymphocytes (%)	19.5 (14.6–25.2), 13	18.5 (13.7–24.0), 79	0.562
Lactate dehydrogenase (U/L)	421 ± 221, 9	272 ± 120, 74	0.002
C-reactive protein (mg/L)	213.6 (185.5–245.5), 16	14.5 (4.0–51.2), 86	<0.001
Ferritin (ng/mL)	918 (795–1450), 13	502 (282–659), 34	0.016
Prothrombin time (s)	13.8 (13.3–14.5), 7	13.1 (12.3–14.1), 50	0.114
D-dimer (μg/mL)	1.841 (1.24–22.5), 11	0.7 (0.5–1.2), 41	0.002
Troponin (ng/mL)	0.11 (0.09–0.37), 13	0.02 (0.01–0.06), 42	<0.001
Creatine kinase-MB (U/L)	56.5 (28.8–96.8), 8	65.0 (37.5–85.8), 72	0.795

Data are n (%), median (IQR), or mean ± SD, n if fewer patients had laboratory results available than the total study population.

Table 2
Characteristics of lung abnormalities on chest computed tomography

	Clinical deterioration or death		P value
	Yes (N = 23)	No (N = 86)	
Lung abnormality			
Only ground-glass opacities	0 (0.0)	21 (24.4)	0.008
Only consolidation	0 (0.0)	1 (1.2)	0.603
Ground-glass opacities and consolidation	22 (95.7)	58 (67.4)	0.007
Pleural effusion	7 (30.4)	8 (9.3)	0.009
Emphysema	3 (13.0)	5 (5.8)	0.238
Fibrosis	2 (8.7)	3 (3.5)	0.289
None	1 (4.3)	6 (7.0)	0.648
Total pneumonia volume (mL)	1040.1 (339.7–2100.7)	282.6 (85.6–520.5)	<0.001
Total pneumonia burden (%)	19.6 (9.3–52.1)	5.9 (1.7–11.6)	<0.001
Laterality[a]			
Unilateral	1 (4.5)	10 (12.5)	0.289
Right	1 (4.5)	6 (7.5)	
Left	0 (0.0)	4 (5.0)	
Bilateral	21 (95.5)	70 (87.5)	
Lobar distribution[a]			
Right upper lobe	21 (26.3)	65 (81.3)	0.105
Right medial lobe	20 (25.0)	64 (80.0)	0.235
Right lower lobe	22 (27.5)	73 (91.3)	0.151
Left upper lobe	20 (25.0)	68 (85.0)	0.476
Left lower lobe	21 (26.3)	72 (90.0)	0.424
Lobar involvement[a]			
1 lobe	0 (0.0)	5 (6.3)	0.478
2 lobes	1 (4.5)	5 (6.3)	
3 lobes	1 (4.5)	7 (8.8)	
4 lobes	1 (4.5)	9 (11.3)	
5 lobes	19 (86.4)	54 (67.5)	
Axial distribution[a]			
Central	0 (0.0)	0 (0.0)	0.046
Peripheral	6 (27.3)	41 (51.3)	
Diffuse	16 (72.7)	39 (48.8)	

[a] calculated for patients with presence of COVID-19 pneumonia (n = 102).

3.2. Chest CT measurements

The median time from chest CT to positive RT-PCR testing was 0 (IQR 0–3) days. Breathing artifacts were observed in 18 (16.5%) cases. The prevalence and distribution of lung abnormalities were comparable between patients with and without the primary outcome, apart from pleural effusions (30.4% vs 9.3%, p = 0.009) being more common in patients with clinical deterioration/death (Table 2). Patients with deterioration/death had higher quantitative pneumonia burden compared to those

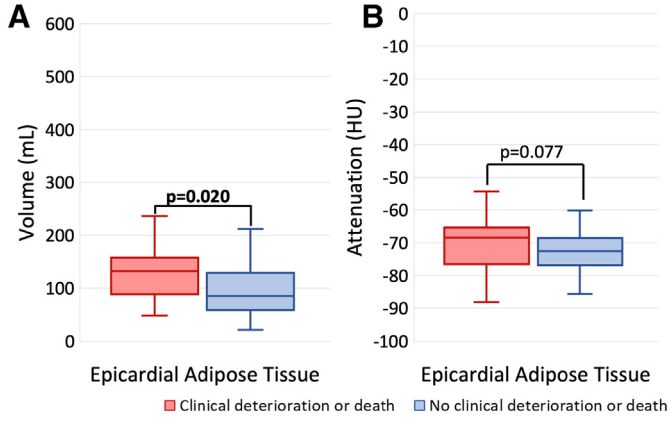

Fig. 3. Differences in epicardial adipose tissue volume (A) and attenuation (B) in patients with and without clinical deterioration or death.

Table 3
Multivariable associations of clinical variables and epicardial adipose tissue with total pneumonia burden (%).

	β-coefficient	Standard Error	95% CI	P value
Age	0.1	0.2	−0.3–0.5	0.552
Male sex	−9.3	4.4	−18.0 to −0.7	0.035
Diabetes mellitus	8.9	5.6	−9.9–8.4	0.116
Hypertension	−0.8	4.6	−2.3–20.0	0.863
Smoking history	−5.2	4.1	−13.4–3.0	0.210
Chronic lung disease	−2.7	5.6	−13.8–8.5	0.637
History of heart failure	1.2	6.6	−12.0–14.3	0.862
Presence of coronary artery disease	−1.5	5.6	−12.7–9.6	0.785
Epicardial adipose tissue volume (mL)[a]	10.6	3.6	3.4–117.8	0.005
Epicardial adipose tissue attenuation (HU)[b]	5.2	1.9	1.5–8.9	0.004

[a] Odds ratios are per 2-fold increase/doubling of the variable.
[b] Odds ratios are per 5 HU increase.

without (19.6% [IQR 9.3–52.1%] vs 5.9% [1.7–11.6%], $p < 0.001$). EAT volume was higher in patients with versus without the primary outcome (132.2 mL [IQR 88.4–157.6 mL] vs 84.9 mL [IQR 58.3–128.6 mL], $p = 0.020$; Fig. 3A). Median EAT attenuation in patients with versus without the primary outcome was −68.4 HU (IQR −76.4 – −65.8) vs −73.0 HU (IQR −76.8 – −68.6), with a trend toward statistical significance ($p = 0.077$; Fig. 3B).

3.3. EAT and extent of COVID-19 pneumonia

In bivariate analysis, EAT volume was positively correlated with total pneumonia burden ($r = 0.29$, $p = 0.006$). In multivariable linear regression adjusted for clinical parameters, the total pneumonia burden was independently associated with EAT volume ($\beta = 10.6$, 95% CI 3.4–17.8, $p = 0.005$) and attenuation ($\beta = 5.2$, 95% CI 1.5–8.9, $p = 0.004$; Table 3)

3.4. EAT as a predictor of clinical deterioration in COVID-19 patients

In multivariable logistic regression analysis, EAT volume (OR 5.1 [95% CI 1.8–14.1] per doubling $p = 0.011$) and EAT attenuation (OR 3.4 [95% CI 1.5–7.5] per 5 Hounsfield unit increase, $p = 0.003$) were independent predictors of clinical deterioration or death, as were total pneumonia burden (OR 2.5, 95% CI 1.4–4.6, $p = 0.002$), chronic lung disease (OR 1.3 [95% CI 1.1–1.7], $p = 0.011$), and history of heart failure (OR 3.5 [95% 1.1–8.2], $p = 0.037$) (Table 4).

3.5. Correlation of EAT with serum biomarkers and clinical variables

Bivariate correlations between CT parameters, serum biomarkers, and clinical variables are presented in Table 5. EAT volume had a moderate correlation with BMI and serum levels of lactate dehydrogenase and CRP; and a weak correlation with creatine kinase-MB levels and total pneumonia volume and burden. EAT attenuation was inversely correlated with lactate dehydrogenase levels.

4. Discussion

In this international multicenter study of patients with COVID-19, we examine the relationship between EAT quantified from chest CT with the extent of pneumonia and adverse outcomes in patients with COVID-19. We demonstrate that: (1) EAT volume and attenuation associate with the quantitative burden of COVID-19 pneumonia; and (2) an increasing EAT volume or attenuation independently predict clinical deterioration or death.

Obesity has been identified as a risk factor for hospitalization and mechanical ventilation in acute respiratory illnesses such as H1N1 influenza [36], and a similar trend is emerging in patients with COVID-19. Evidence shows that any degree of obesity (BMI ≥30 kg/m^2) associates with more advanced disease including respiratory and multiorgan failure in COVID-19, and morbid obesity (BMI ≥40 kg/m^2) confers a significantly worse prognosis compared to normal weight [7–11]. Although traditionally used to define obesity, BMI ≥30 kg/m^2 remains an indirect marker of excess body fat and does not account for the substantial regional and phenotypic variation in fat depots [14]. Several reports have shown abdominal visceral fat area quantified on CT to associate with critical illness in patients with COVID-19 [26,37], however data on thoracic fat depots are lacking. It is established that CT-derived EAT measures correlate strongly with abdominal visceral adiposity and metabolic risk factors [38] and associate with coronary atherosclerosis [39]. Prior studies utilizing manual measurements of EAT thickness on chest CT of COVID-19 patients have failed to show an association of this metric with extent of pneumonia or clinical course [26,27]. By contrast, our fully automated, three-dimensional measurement of EAT provided a more comprehensive assessment of this visceral fat depot, with the resultant EAT volume associating with pneumonia burden. Furthermore, EAT attenuation quantified by this method was predictive of clinical deterioration or death, independently of cardiovascular risk factors and coronary artery disease. This is consistent with a recent report showing EAT attenuation to be higher in patients with clinically severe or critical COVID-19 compared to those with mild or moderate disease [27].

Mechanistically, EAT may exert a direct, local effect on the neighboring lungs and/or contribute to the augmented systemic inflammatory response to COVID-19 [40,41]. An increasing EAT volume has been

Table 4
Association of clinical and CT parameters with the risk of clinical deterioration or death in univariable and multivariable* logistic regression analysis.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.1 (1.0–1.2)	0.001	–	
Male sex	1.7 (0.62–4.9)	0.292	–	
Diabetes mellitus	5.1 (1.8–14.5)	0.002	–	
Hypertension	1.2 (1.0–1.3)	0.006	–	
Smoking history	0.9 (0.3–2.4)	0.782	–	
Chronic lung disease	1.1 (0.9–1.2)	0.136	1.3 (1.1–1.7)	0.011
History of heart failure	6.8 (1.5–14.6)	<0.001	3.5 (1.1–8.2)	0.037
History of coronary artery disease	4.1 (1.3–13.1)	0.017	–	
Epicardial adipose tissue volume (mL)[a]	2.9 (1.2–7.2)	0.020	5.1 (1.8–14.1)	0.011
Epicardial adipose tissue attenuation (HU)[b]	1.3 (0.9–1.8)	0.114	3.4 (1.5–7.5)	0.003
Total pneumonia burden (%)[a]	2.3 (1.5–3.5)	<0.001	2.5 (1.4–4.6)	0.002

* All variables entered into multivariable logistic regression with backward stepwise selection at a Wald p-value of 0.1. The final model containing statistically significant variables is shown.
[a] Odds ratios are per 2-fold increase/doubling of the variable.
[b] Odds ratios are per 5 HU increase.

Table 5
Correlation matrix between investigated variables.

	EAT volume	EAT attenuation	Age	Male gender	Body Mass Index	Lymphocytes	Lactate dehydrogenase	C-reactive protein	Ferritin	Prothrombin time	D-dimer	Troponin	Creatine kinase	Total pneumonia volume	Total pneumonia burden
EAT volume	1.000														
EAT attenuation	−0.672*	1.000													
Age	0.378*	−0.036	1.000												
Male gender	0.221*	0.130	0.126	1.000											
Body mass index	0.369*	−0.193	0.047	0.092	1.000										
Lymphocytes	−0.157	0.065	−0.282*	−0.096	−0.041	1.000									
Lactate dehydrogenase	0.361*	−0.293*	0.141	0.107	0.044	−0.095	1.000								
C-reactive protein	0.450*	−0.152	0.400*	0.130	0.212	−0.125	0.482*	1.000							
Ferritin	0.005	0.064	−0.120	0.132	0.061	−0.015	0.181	0.198	1.000						
Prothrombin time	0.181	−0.144	0.277†	0.016	−0.113	0.211	0.167	0.365*	−0.051	1.000					
D-dimer	0.180	0.206	0.270	0.243	0.003	0.057	−0.032	0.409*	0.165	0.209	1.000				
Troponin	0.118	0.076	0.201	−0.136	0.043	0.034	0.202	0.391*	0.048	0.052	0.390†	1.000			
Creatine kinase-MB	0.167	−0.150	0.030	0.104	0.115	−0.054	0.185	0.092	0.029	0.067	0.232	0.196	1.000		
Total pneumonia volume	0.297*	0.018	0.319*	0.133	0.193	−0.053	0.313*	0.372*	0.346*	0.156	0.468*	0.265	−0.086	1.000	
Total pneumonia burden	0.286*	0.022	0.336*	0.002	0.244	−0.066	0.319*	0.388*	0.285†	0.163	0.467†	0.233	−0.061	0.967*	1.000

† Correlation is significant at the 0.01 level.
* Correlation is significant at the 0.05 level.

shown to associate with reduced lung function in healthy individuals [15,16] and disease severity in those with chronic lung conditions [18,42]. The close proximity of EAT to the pulmonary artery potentially enables direct diffusion of inflammatory mediators into the pulmonary circulation [43], which may then exert vasocrine or paracrine effects on the lung tissue. This local inflammation could partly explain the association of EAT measures with quantitative burden of COVID-19 pneumonia in our study. Certainly, it is established that EAT has a pathophysiological influence on adjacent structures such as the coronary arteries and myocardium, promoting atherosclerosis and fibrosis [44]. The release of proinflammatory cytokines from EAT into the general circulation may contribute to the systemic inflammatory state in COVID-19; systemic inflammation, in turn, promotes accumulation of EAT, creating a positive feedback loop [18,45–47]. EAT inflammation may be reflected by a higher CT attenuation of this fat depot [48]. Furthermore, angiotensin-converting enzyme 2 (ACE-2), used by SARS-CoV-2 to enter host cells, is expressed in several different cell-lines including adipocytes [49]. Given that ACE-2 upregulation is seen in adipocytes of patients with obesity and diabetes, EAT may serve as an important viral reservoir [50]. Finally, visceral fat accumulation, associated with reduced testosterone levels especially in older males, may influence the pathophysiology of COVID-19 through dysregulation of the growth hormone (GH)–insulin-like growth factor 1 (IGF1) axis [51]. It has been recently hypothesized that GH insufficiency may contribute to gender-related differences in COVID-19 [52]. Indeed, our study showed an association of EAT, age, and male gender with the extent of pneumonia, underscoring the complex interplay between the endocrine and immune systems.

The integration of EAT volume measurements into clinical risk scores for patients with COVID-19 has the potential to enhance in-hospital outcome prediction. Our deep learning-based method of EAT quantification from routine chest CT is rapid (<3 min per case); however more studies are required to determine whether this approach is applicable to different COVID-19 populations. Anti-inflammatory agents have shown promising results in hospitalized patients with COVID-19 [53,54], and their effects in obese versus normal-weight patients or patients with high versus low EAT volumes should be explored in future studies.

Our study has several limitations. First, different patient profiles and treatment protocols between countries may have resulted in heterogeneity in COVID-19 pneumonia severity or in-hospital outcomes. Second, chest CT indications and acquisition protocols were not standardized across centers. Third, our sample size was relatively small and larger studies are needed to validate our findings. Fourth, BMI measurements were not obtained in all patients and thus we were unable to adjust for the potentially confounding effect of this obesity measure in our multivariable models. Finally, levels of serum biomarkers such as CRP, lactate dehydrogenase, and troponin were not uniformly available and thus not included in our risk prediction models to assess the independent effects of systemic inflammation or myocardial injury on outcomes; further studies are needed to assess these relationships.

5. conclusion

EAT parameters quantified from chest CT are independently associated with extent of pneumonia and adverse outcomes in patients with COVID-19, lending support to its use in clinical risk stratification.

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CRediT authorship contribution statement

Kajetan Grodecki: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Andrew Lin:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Aryabod Razipour:** Investigation, Data curation, Writing - review & editing. **Sebastien Cadet:** Formal analysis, Software, Writing - review & editing. **Priscilla A. McElhinney:** Investigation, Data curation, Writing - review & editing. **Cato Chan:** Resources, Data curation, Writing - review & editing. **Barry D. Pressman:** Resources, Data curation, Writing - review & editing. **Peter Julien:** Resources, Data curation, Writing - review & editing. **Pal Maurovich-Horvat:** Resources, Data curation, Writing - review & editing. **Nicola Gaibazzi:** Resources, Data curation, Writing - review & editing. **Udit Thakur:** Resources, Data curation, Writing - review & editing. **Elisabetta Mancini:** Resources, Data curation, Writing - review & editing. **Cecilia Agalbato:** Resources, Data curation, Writing - review & editing. **Robert Menè:** Resources, Data curation, Writing - review & editing. **Gianfranco Parati:** Resources, Data curation, Writing - review & editing. **Franco Cernigliaro:** Resources, Data curation, Writing - review & editing. **Nitesh Nerlekar:** Resources, Data curation, Writing - review & editing. **Camilla Torlasco:** Resources, Data curation, Writing - review & editing. **Gianluca Pontone:** Resources, Data curation, Writing - review & editing. **Piotr J. Slomka:** Software, Resources, Data curation, Writing - review & editing. **Damini Dey:** Conceptualization, Methodology, Formal analysis, Software, Resources, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154436.

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