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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Association of epicardial adipose tissue with the severity and adverse clinical outcomes of COVID-19: A meta-analysis

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ABSTRACT

Objectives: Epicardial adipose tissue (EAT) has been proposed to be an independent predictor of visceral adiposity. EAT measures are associated with coronary artery disease, diabetes, and chronic obstructive pulmonary disease, which are risk factors for COVID-19 poor prognosis. Whether EAT measures are related to COVID-19 severity and prognosis is controversial.

Methods: We searched 6 databases for studies until January 7, 2022. The pooled effects are presented as the standard mean difference (SMD) or weighted mean difference with 95% confidence intervals (CIs). The primary end point was COVID-19 severity. Adverse clinical outcomes were also assessed.

Results: A total of 13 studies with 2482 patients with COVID-19 were identified. All patients had positive reverse transcriptase-polymerase chain reaction results. All quantitative EAT measures were based on computed tomography. Patients in the severe group had higher EAT measures compared with the nonsevere group (SMD = 0.74, 95% CI: 0.29–1.18, $P = 0.001$). Patients with hospitalization requirement, requiring invasive mechanical ventilation, admitted to intensive care unit, or with combined adverse outcomes had higher EAT measures compared to their controls (all $P < 0.001$).

Conclusions: EAT measures were associated with the severity and adverse clinical outcomes of COVID-19. EAT measures might help in prognostic risk stratification of patients with COVID-19.

Introduction

More and more COVID-19 cases have been confirmed since December 2019. As of December 21, 2021, there have been over 273 million confirmed cases and over 5.3 million deaths worldwide (World Health Organization, 2021). Hospitals, especially intensive care units (ICU), are currently overcrowded in some countries. Determining how to assess the severity quickly and predict the outcomes of COVID-19 (such as the need for hospitalization) after patients visiting an outpatient or emergency department began a research goal for doctors, which could efficiently allocate medical resources and help doctors make treatment-related decisions.

Early studies have revealed that obesity with a higher body mass index (BMI) is a risk factor for developing a critical condition in COVID-19 (Chang et al., 2020, Chu et al., 2020, Huang et al., 2020). Although widely used to assess obesity, BMI was not always an accurate prediction of adverse clinical outcomes of COVID-19 (Caussy et al., 2020, Yang et al., 2020). This suggested that the relationship between obesity and the severity and mortality of COVID-19 is more complex. The underlying pathophysiologic mechanisms remain unclear.

Epicardial adipose tissue (EAT), an ectopic heart adipose, modulates the metabolic environment of both the coronary arteries and myocardium. EAT has close relationships with coronary artery disease, metabolic syndrome, diabetes, obstructive sleep apnea, and human immunodeficiency virus. Iacobellis et al pioneered the research on EAT (Iacobellis, 2015, Iacobellis et al., 2005). EAT has been proposed as an independent predictor of visceral adiposity and may have a close relationship with adverse clinical outcomes of COVID-19; this was first reported by Malavazos, Goldberger, and Iacobellis in 2020 (Malavazos et al., 2020).

EAT can be measured by chest computed tomography (CT) scan and echocardiography. EAT thickness, volume, and density/attenuation can be easily and precisely measured by CT scan

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using commercial software. Image analysis took approximately 3 minutes per patient (Conte et al., 2021). Several studies have evaluated the relationship between EAT measures and COVID-19 severity (Deng et al., 2020, Iacobellis et al., 2020, Watanabe et al., 2020). However, small sample sizes and potential confounders, such as differences in EAT measures, can affect the strength of previous evidence. Therefore, this meta-analysis of studies was conducted to provide a more comprehensive summary of currently available research to explore the association of EAT measures with the severity and clinical outcomes of COVID-19.

Methods

We followed a reporting guideline (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA) to perform this study. A review protocol (CRD42022302104) with search strategy was registered in the PROSPERO international prospective register of systematic reviews.

Search strategy

Two independent investigators (KL and XW) independently searched PubMed, MEDLINE, Web of Science, Embase, Cochrane library, and medRxiv.org from database inception to January 7, 2022 to identify relevant studies. The following search keywords included "COVID-19" and "epicardial adipose tissue". At the same time, we read the references of articles to find the potential literature which may meet the criteria.

Study selection and exclusion

Two researchers (KL and XW) independently screened the titles and abstracts for eligibility. Full papers were assessed to confirm disagreement in existence according to the exclusion criteria by the 2 researchers. Disagreements were discussed and resolved by involving a third reviewer (GS) for adjudication.

Original studies were eligible if the following criteria were met: (i) COVID-19 with different related clinical outcomes or different severity, (ii) quantitative assessment of EAT measures (EAT thickness, volume, or attenuation) by CT or echocardiography as soon as possible after presenting to the hospital, and (iii) text in English available. Original studies were ineligible if the following criteria existed: (i) reviews, case reports, or case series; (ii) did not report the data necessary for calculating the mean and standard deviation of EAT measures; and (iii) animal studies. If there were several publications from the same study, the study with the most cases and relevant information was included.

The extracted data included the first author of involved studies, year of publication, country, participant number, gender, age, BMI, EAT measures, and outcomes. Numeric data were gathered directly from tables or, when presented in graphs only, were inferred by digitizing the figure with GetData Graph Digitizer 2.26 (Li et al., 2017). The quality assessment was performed by the Newcastle–Ottawa Scale (NOS) assessment tool.

Clinical outcomes and severity of COVID-19

The clinical outcomes involved in the meta-analysis were death/survival, the need for invasive mechanical ventilation, the need for hospitalization, the need for ICU admission, or combined adverse outcomes. Combined adverse outcomes were the need for ICU admission, invasive mechanical ventilation, vasopressor therapy, or death (Bihan et al., 2021, Grodecki et al., 2021, Phan et al., 2021). In our meta-analysis, severe or critical patients with COVID-19 were grouped into the severe group, and mild or moderate patients with COVID-19 were grouped into the nonsevere group. The severity criteria of the involved studies were shown in **Supplementary Table S1**.

Statistical analysis

The pooled effects are presented as the weighted mean difference (WMD) or standard mean difference (SMD) with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic. If there was no heterogeneity ($P > 0.1$ or $I^2 < 50\%$), a fixed-effects model was used to estimate the pooled effect; otherwise, a random-effects model was used. When heterogeneity existed, we conducted subgroup analyses based on "EAT measures" or "type of clinical outcomes". Sensitivity analyses were directed to assess the influence of the individual study on the overall estimate. We analyzed the symmetry of a funnel plot to evaluate possible small sample effects and used Begg and Egger tests to evaluate publication bias in the included studies. A p-value < 0.05 was considered statistically significant for asymmetry. Trim-and-fill analysis was performed to 'normalize' the asymmetric funnel plot. Statistical analyses were performed using Stata (version 16.0; StataCorp, College Station, TX, USA).

Results

Search selection

We had searched potentially relevant publications from 6 sources. After applying the inclusion and exclusion criteria, 13 studies were identified (Abrishami et al., 2021, Bihan et al., 2021, Conte et al., 2021, Deng et al., 2020, Eslami et al., 2021, Grodecki et al., 2021, Guarisco et al., 2021, Iacobellis et al., 2020, Phan et al., 2021, Sevilla et al., 2022, Slipczuk et al., 2021, Turker Duyuler et al., 2021, Watanabe et al., 2020) (**Figure 1**).

Characteristics of studies

The baseline characteristics of the included studies are shown in **Table 1**. All studies were published in these 3 years. Studies were conducted in Europe (France, Italy, and Spain), North America (USA), and Asia (China, Iran, and Turkey). A total of 2482 patients with COVID-19 were included, all of whom had positive reverse transcriptase-polymerase chain reaction results. All quantitative EAT measures in these 13 studies were CT-based. A total of 8 studies evaluated the EAT volume, 8 with EAT attenuation, and 3 with EAT thickness. A total of 6 studies evaluated the association between EAT measures and the severity of COVID-19. A total of 10 studies evaluated the association between EAT measures and clinical outcomes of COVID-19. The NOS score ranged from 7–9, indicating no low-quality study was involved (**Supplementary Table S2**).

Association of EAT measures with the severity of COVID-19 and subgroup analysis

A total of 1128 patients (336 in the severe group and 792 in the nonsevere group) were involved in the quantitative data synthesis. Patients in the severe group had higher EAT measures compared to the nonsevere group (SMD = 0.74, 95% CI: 0.29–1.18, $P = 0.001$).

To investigate the possible sources of this heterogeneity ($I^2 = 92.6\%$, $P < 0.001$), we carried out the subgroup analysis (**Figure 2**). However, heterogeneity did not decrease after stratification by the type of EAT measures. Subgroup analysis indicated that significant results were observed in the EAT volume and EAT thickness subgroups (SMD = 0.62, 95% CI: 0.14–1.11, $P = 0.012$; SMD = 1.22, 95% CI: 0.97–1.47, $P < 0.001$).

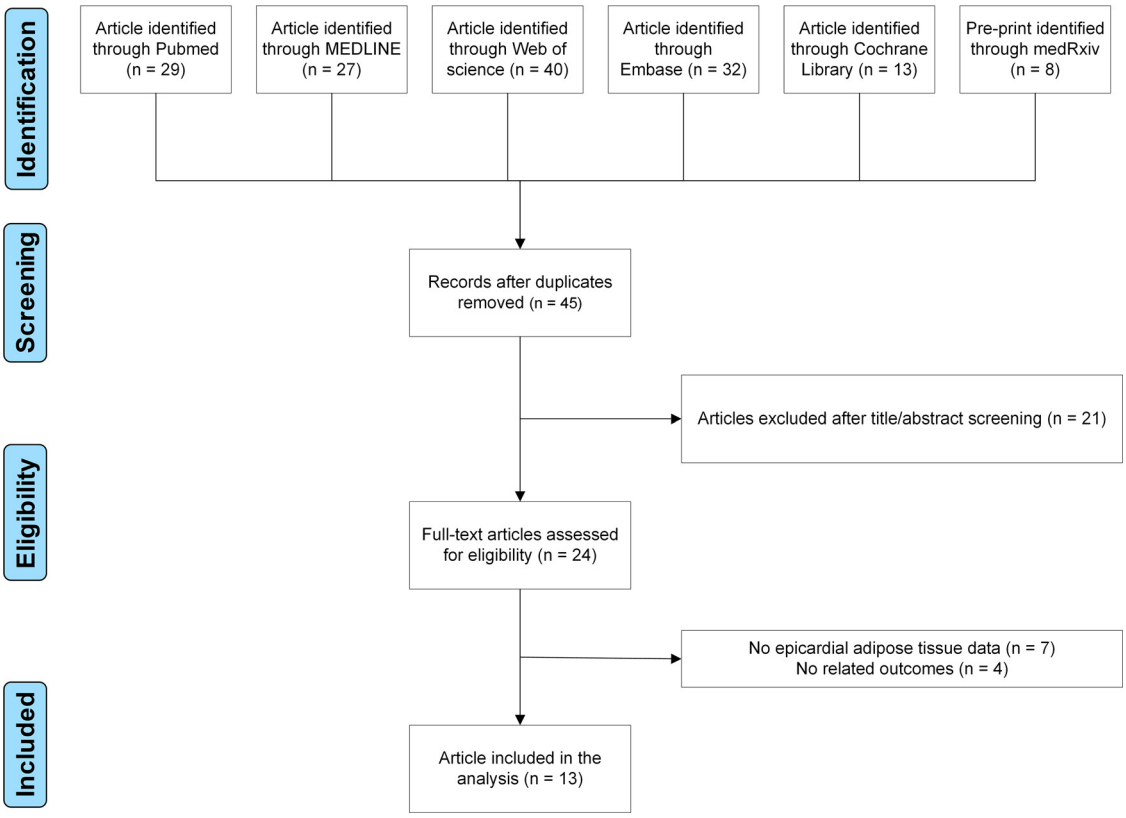

Figure 1. Flow-chart of study selection.

Table 1
The baseline characteristics of the included studies

Study	Year	Country	Participant number	Male (%)	Age (year)	BMI(kg/m^2)	EAT measures	Outcomes	NOS score
Deng	2020	China	65	55.4	34.5±5.8	24.0±4.4	Volume, attenuation	Severity	9
Iacobellis	2020	Italy	41	73.2	67.0±13.0	26.9±4.4	Attenuation	Severity, ICU, IMV	7
Watanabe	2020	Italy	150	64.7	64.2±15.7	NR	Thickness	IMV, ICU, hospitalization	8
Abrishami	2021	Iran	100	68.0	55.5±15.2	NR	Volume, attenuation	Survival	8
Bihan	2021	France	100	63.0	61.8±16.2	28.9±6.2	Volume	Severity, combined adverse outcomes	9
Conte	2021	Italy	192	76.0	60.0±12.5	26.7±3.9	Volume, attenuation	Severity	9
Eslami	2021	Iran	87	65.5	54.6±15.3	NR	Thickness, attenuation	Survival	7
Grodecki	2021	USA, Italy	109	62.4	63.7±16.0	26.2±3.9	Volume, attenuation	Combined adverse outcomes	9
Guarisco	2021	Italy	229	57.8	62.1±17.4	27.2±4.6	Volume, attenuation	Severity	9
Phan	2021	France	81	72.8	66.0±11.1	27.0±5.2	Volume	Survival, combined adverse outcomes	9
Slipczuk	2021	USA	493	49.5	70.0±7.4	27.3±6.4	Volume	Survival	9
Turker Duyuler	2021	Turkey	504	56.6	53.8±18.9	26.2±2.7	Thickness	Severity, ICU, hospitalization	8
Sevilla	2022	Spain	331	56.0	71.0±11.0	NR	Attenuation	Survival, IMV, ICU	7

BMI, body mass index; EAT, epicardial adipose tissue; IMV, invasive mechanical ventilation; ICU, intensive care unit admission; NR, no reported; NOS, New castle Ottawa Scale.

Subgroup analysis for the association of EAT measures with clinical outcomes of COVID-19

After stratification by the type of clinical outcomes, patients with combined adverse outcomes had higher EAT volume (in milliliters) than those without combined adverse outcomes (WMD = 49.61, 95% CI: 31.45–67.78, $P < 0.001$, **Figure 3**).

Patients admitted to ICU had higher EAT attenuation compared with patients without ICU admission (WMD = 13.07, 95% CI: 8.07–18.06, $P < 0.001$, **Figure 4**). Patients requiring IMV had higher EAT attenuation than patients without IMV requirement (WMD = 13.07, 95% CI: 8.07–18.06, $P < 0.001$, **Figure 4**).

The EAT thickness (in millimeters) was significantly increased in the patients admitted to ICU than the patients without ICU admission (WMD = 0.89, 95% CI: 0.66–1.12, $P < 0.001$, **Figure 5**). Furthermore, the EAT thickness was significantly increased in patients with hospitalization requirements than patients without (WMD = 0.74, 95% CI: 0.45–1.03, $P < 0.001$, **Figure 5**).

There was no difference of EAT measures between the nonsurvivor and survivor group (EAT volume: WMD = 13.43,

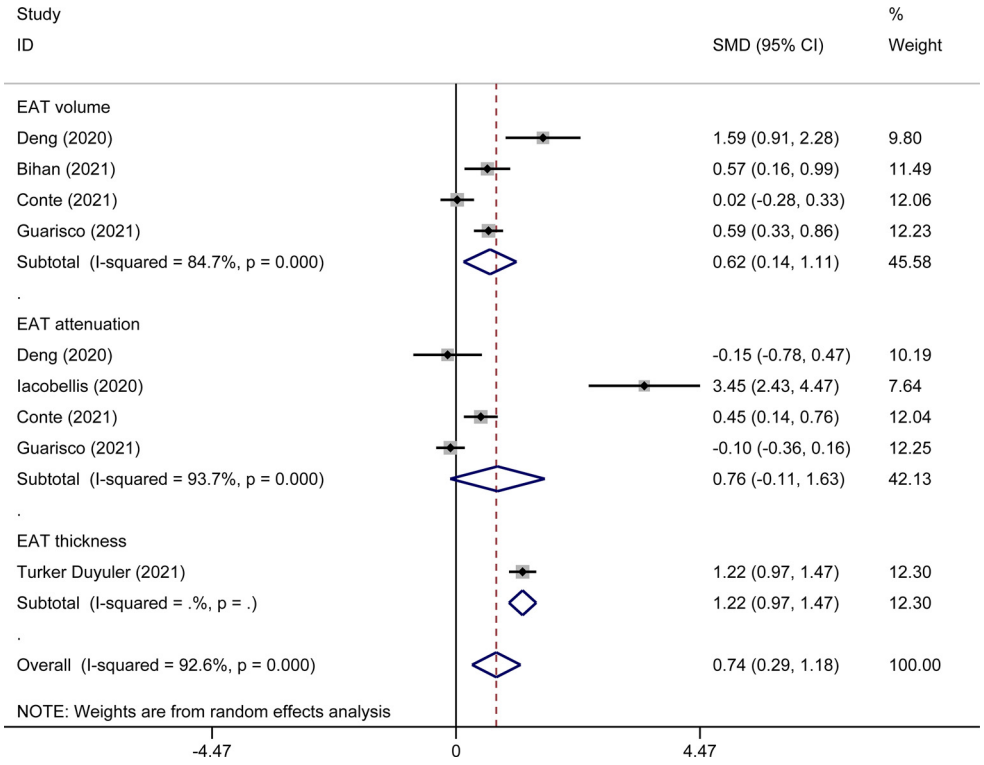

Figure 2. Subgroup analysis of standard mean difference in EAT measures between patients with severe COVID-19 and patients with nonsevere COVID-19. EAT, epicardial adipose tissue

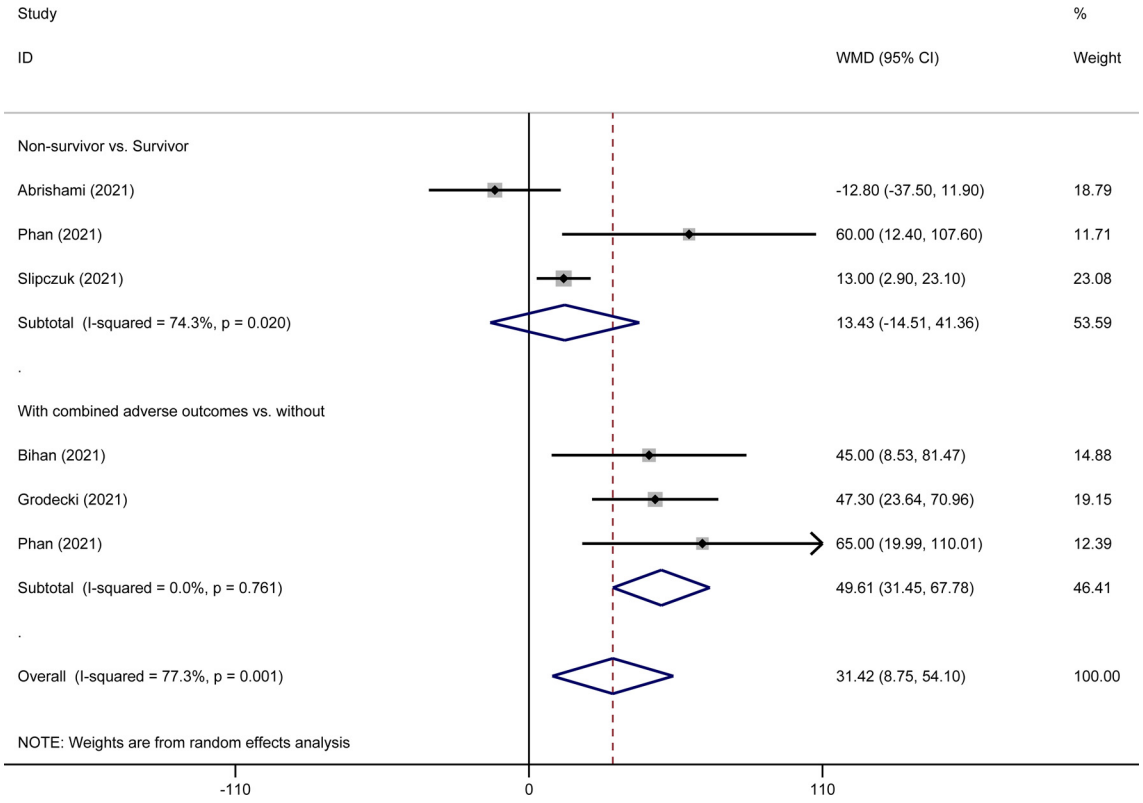

Figure 3. Subgroup analysis of weighted mean difference in EAT volume between different clinical outcomes of COVID-19. EAT, epicardial adipose tissue.

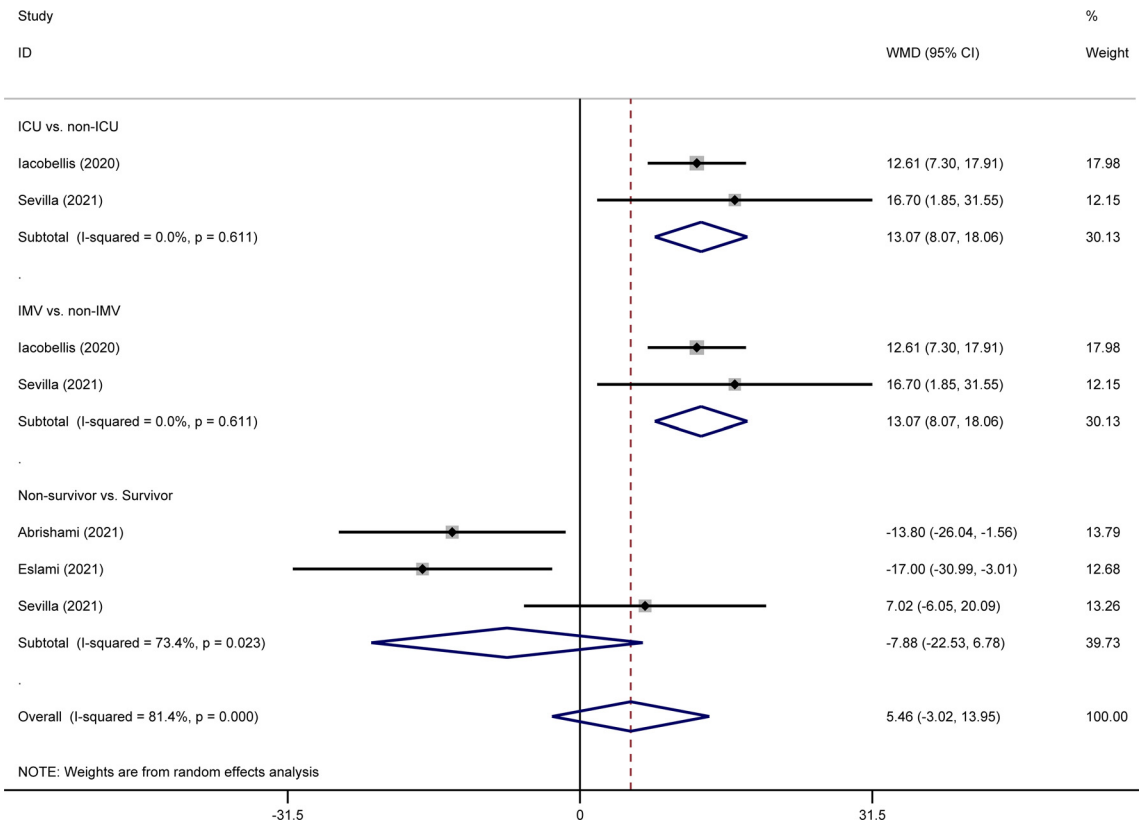

Figure 4. Subgroup analysis of weighted mean difference in EAT attenuation between different clinical outcomes of COVID-19. EAT, epicardial adipose tissue.

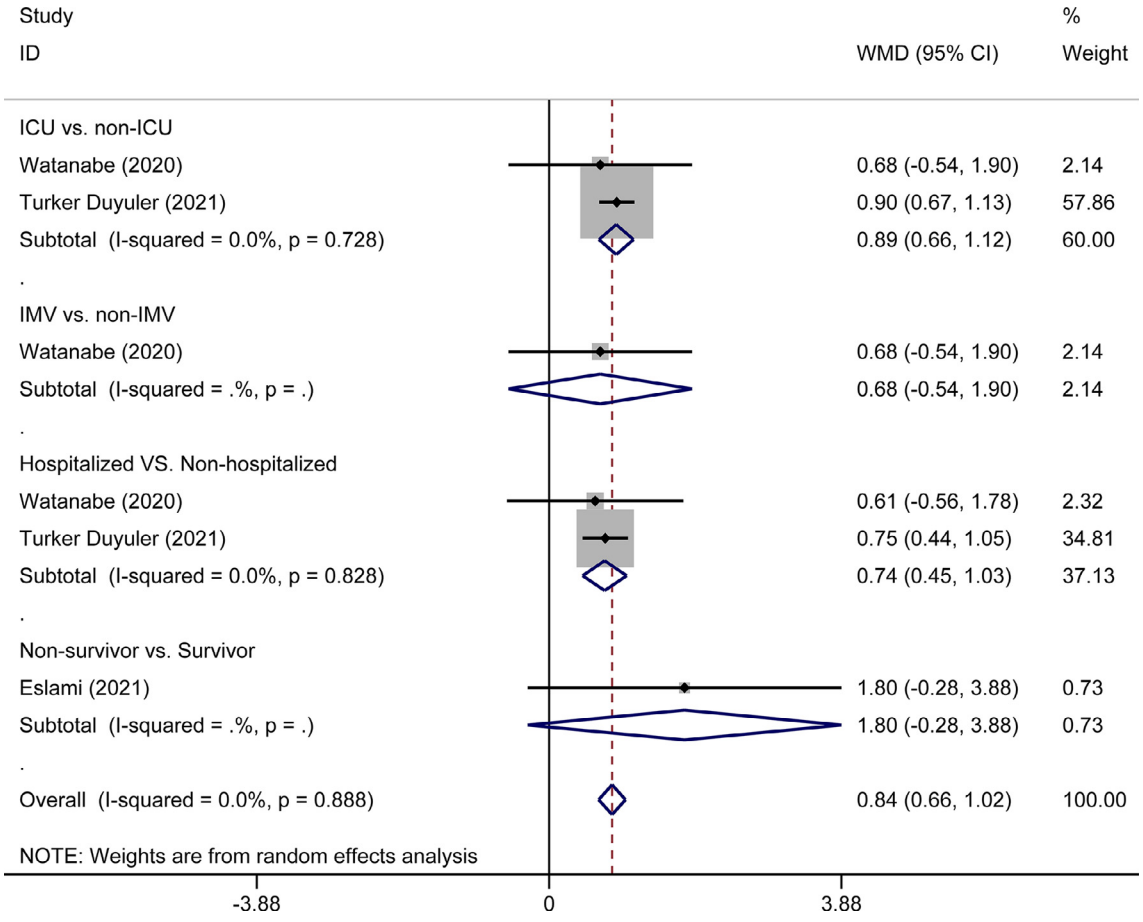

Figure 5. Subgroup analysis of weighted mean difference in EAT thickness between different clinical outcomes of COVID-19. EAT, epicardial adipose tissue.

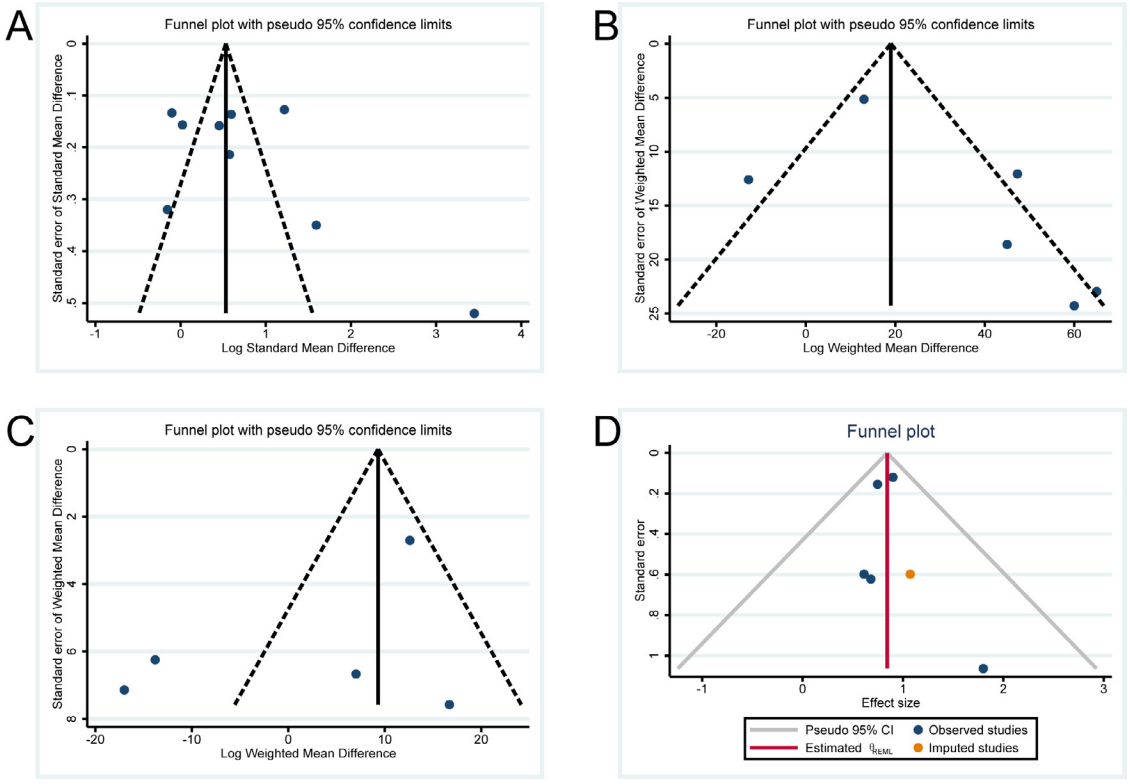

Figure 6. Evaluation of publication bias using the funnel plot. (A) EAT measures between severe and nonsevere groups. (B) EAT volume between different clinical outcomes of COVID-19. (C) EAT attenuation between different clinical outcomes of COVID-19. (D) Trim-and-fill analysis for EAT thickness between different clinical outcomes of COVID-19. EAT, epicardial adipose tissue.

95% CI: -14.51–41.36, $P = 0.346$; EAT attenuation: WMD = -7.88, 95% CI: -22.53–6.78, $P = 0.292$; EAT thickness: WMD = 1.80, 95% CI: -0.28–3.88, $P = 0.091$).

Sensitivity analysis and publication bias

To evaluate the robustness of the results, sensitivity analyses were performed by sequentially removing each study. No apparent change occurred for most outcomes when an individual study was omitted.

No publication bias was observed in our evaluation of the funnel plots for EAT measures with the severity of COVID-19, and this finding was confirmed by Begg ($P = 0.466$) and Egger ($P = 0.991$) tests. No publication bias was observed in our evaluation of the funnel plots for EAT volume with the clinical outcomes of COVID-19, and this finding was confirmed by Begg ($P = 0.707$) and Egger ($P = 0.985$) tests. No publication bias was observed in our evaluation of the funnel plots for EAT attenuation with the clinical outcomes of COVID-19, and this finding was confirmed by Begg ($P = 0.764$) and Egger ($P = 0.069$) tests. However, an obvious publication bias was revealed in our evaluation of the funnel plots for EAT attenuation with the clinical outcomes of COVID-19, confirmed by Begg ($P = 0.348$) and Egger ($P = 0.001$) tests; Thus, the trim-and-fill method was used to adjust the publication bias. After trimming, the results were similar, indicating that the results were statistically reliable (WMD = 0.84, 95% CI: 0.66–1.02, **Figure 6**).

Discussion

To the best of our knowledge, this is the first meta-analysis that comprehensively summarized the association of EAT measures with the severity of COVID-19. EAT measures had a close relationship with adverse clinical outcomes of COVID-19 and thus became a risk stratification tool for patients with COVID-19. The results were confirmed by subgroup analysis, sensitivity analysis, and publication bias test.

A previous study has confirmed that obesity increased the infection severity in patients with 2009 influenza A virus infection (Van Kerkhove et al., 2011). Similar results were revealed in patients with COVID-19 (Du et al., 2021, Pranata et al., 2021b). BMI is a simple index and commonly used to classify overweight and obesity in adults. Recent meta-analysis papers demonstrated that a nonlinear relationship was observed between BMI and adverse clinical outcomes in patients with COVID-19 (Du et al., 2021, Pranata et al., 2021b). One of the studies revealed that the odds ratios for overweight patients and obesity patients were 1.02 (95% CI:0.99–1.05) and 1.09 (95% CI:1.04–1.15) when using BMI of 20 kg/m^2 as the reference (Pranata et al., 2021b). Overweight patients with COVID-19 with increased BMI probably didn't have a higher risk of adverse outcomes than normal-weight controls, consistent with several recently published studies (Kananen et al., 2021, Tamara and Tahapary, 2020, van Son et al., 2021). That conclusion also suggested that the relationship between body fat and the severity/adverse outcome of COVID-19 is more complex.

There are some anthropometric tools that are used as BMI complements to determine obesity, including waist circumference, waist-to-hip ratio, waist-to-height ratio, or visceral adiposity parameters (Sommer et al., 2020). Researchers found the Edmonton Obesity Staging System, a clinical classification tool, was associated with adverse COVID-19 outcomes. This system distinguished risks beyond BMI (Rodriguez-Flores et al., 2022). The limitation of this system is complicated and may not be suitable for patients who need urgent care. Recently studies have shown that visceral adiposity seems to be a better risk stratification tool in COVID-19, and patients with central obesity might need special attention (Foldi et al., 2021, Pranata et al., 2021a). However, no standard CT

protocol for visceral adiposity measurement (quantified at the different levels) may cause high heterogeneity of studies. Abdominal CT is also not a routine exam for patients with COVID-19.

EAT, as ectopic visceral fat around the heart, makes up for the lack of BMI that does not reflect the mass of the visceral fat (Hamdy et al., 2006). EAT is a potential source of inflammatory mediators, including tumor necrosis factor-alpha (TNF-alpha), interleukins 1 and 6 (IL-1, IL-6), leptin, and monocyte chemoattractant protein-1, and is a potential marker of systemic inflammation (Shimabukuro et al., 2013, Song et al., 2020). Inflammation plays a major role in the pathogenesis and prognosis of COVID-19 (Feng et al., 2020). Therefore, many studies have begun to verify the hypothesis that there are close relationships between EAT and severity/adverse outcomes of COVID-19.

EAT can be measured by chest CT scan and echocardiography. EAT measurement by echocardiography was first developed by Iacobellis et al (Iacobellis et al., 2003). However, echocardiography can only measure the EAT thickness, and the imaging quality may reduce owing to COVID-19 pneumonia. Chest CT scan is a useful exam for suspected or confirmed patients with COVID-19, both for diagnosis and in clinical decision-making (Garg et al., 2021). Our meta-analysis revealed that EAT measures had a close relationship with the severity and adverse clinical outcomes of COVID-19. Therefore, EAT measures by chest CT scan on admission could be a risk stratification tool for patients with COVID-19. EAT measures were associated with multiple inflammatory biomarkers and PaO_2/FiO_2 ratio, which were proven to be effective predictors of COVID-19 progression (Abrishami et al., 2021, Guarisco et al., 2021). The integration of EAT volume measurements into the clinical risk scores system for patients with COVID-19 can potentially enhance adverse outcome prediction (Conte et al., 2021, Grodecki et al., 2021, Guarisco et al., 2021, Turker Duyuler et al., 2021).

The mechanism of EAT measures in patients with COVID-19 is not clear. EAT may exert the direct/paracrine and indirect/systemic effect in COVID-19. On the basis of the results of existing research (Conte et al., 2021, Grodecki et al., 2021, Watanabe et al., 2020), we propose the following: (i) EAT was associated with coronary artery disease, diabetes, chronic obstructive pulmonary disease, and old age and male sex which were risk factors for COVID-19 poor prognosis (Parohan et al., 2020); (ii) COVID-19 infection could trigger systemic inflammatory response (Coperchini et al., 2020). EAT may transduce this inflammation to the heart (Kim and Han, 2020, Malavazos et al., 2020). Furthermore, EAT may exert a direct effect on the neighboring lungs and enhance systemic inflammatory response to COVID-19 (Moore and June, 2020, Ryan and Caplice, 2020). The EAT, which is near the pulmonary artery, enables direct diffusion of the inflammatory mediators into the pulmonary circulation, which may then exert vasocrine or paracrine effects on the lung tissue (Grodecki et al., 2021); (iii) EAT accumulation caused growth hormone–insulin-like growth factor 1 axis impairment, which usually affects old male patients, may further influence the pathophysiology of COVID-19 (Lubrano et al., 2020); (iv) COVID-19 infection could trigger systemic inflammation, including EAT inflammation. Viruses infect cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in EAT (Couselo-Seijas et al., 2021). A recent animal study found that ACE2 deficiency could worsen EAT inflammation in diet-induced obesity in mice (Patel et al., 2016); and (v) 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 (Grodecki et al., 2021).

Recently, Iacobellis et al. reported that 33 patients with COVID-19 had reduced EAT attenuation after receiving the dexamethasone therapy compared with any of the other therapies (Iacobellis et al., 2021). Therefore, EAT could serve as a therapeutic target for anti-inflammatory treatment in patients with COVID-19. More studies about EAT attenuation in COVID-19 are suggested. For patients with an increased EAT measure, doctors may advise hospitalization and prompt closer clinical observation for the possibility of myocardial injury and/or cardiac dysfunction (Özer et al., 2021, Wei et al., 2020). Both statins and colchicine were proven to decrease EAT (Konwerski et al., 2022). Recent studies have found these 2 drugs may reduce the mortality risk of patients with COVID-19 (Chiu et al., 2021, Diaz-Arocutipa et al., 2021). There are several ongoing clinical trials (such as NCT04472611, NCT04904536, NCT05038449) that evaluate the efficacy and safety of these 2 drugs for patients with COVID-19. Therefore, statins and colchicine may be beneficial to patients with COVID-19 with an increased EAT measure.

Limitations

First, most studies were single-centered. Single race and the small sample size can't be ignored. All these disadvantages could reduce the credibility of the conclusion of this study. Second, high heterogeneity was found in most analyses. Subgroup analysis was performed. No source of heterogeneity was revealed. Third, some underlying confounders may not be adjustable in the involved studies, such as BMI in each group. Fourth, although the publication bias was adjusted by the trim-and-fill method, the scarcity of the involved studies with EAT thickness data may affect the credibility of the conclusion.

Conclusions

The EAT measures were associated with the severity and adverse clinical outcomes of COVID-19. The EAT measures might help in the prognostic risk stratification of patients with COVID-19.

Ethical approval statement

Not applicable.

Funding sours

None.

Conflict of interest

The authors have no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.04.013.

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