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Epikardiales, subkutanes und viszerales Fettgewebe als prognostische Marker bei diversen Erkrankungen

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(nachfolgend Originalarbeit 1 genannt)

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Publikation 3:
Barajas.F, Zeller Y, Wolleschak Y, Hinnerichs M, Feria P, Mougiakakos D, **Aghayev A,** Kardas H, Mikusko M, Borggrefe J, Surov A. Low subcutaneous adipose tissue and myosteatosis are prognostic factors after allogeneic hematopoietic stem cell transplantation. Clinical Nutrition ESPEN. 2024 March 29. doi: 10.1016/j.clnesp.2024.03.032.(nachfolgend Originalarbeit 3 genannt)

Kurzreferat

In dieser kumulativen Dissertation untersuchen wir die prognostische Bedeutung des epikardialen und subkutanen Fettgewebes (EAT und SAT) bei verschiedenen Patientengruppen, einschließlich solcher mit akuter Lungenembolie, COVID-19 und nach allogener hämatopoetischer Stammzelltransplantation (allo-HSCT). Unsere Studien basieren auf retrospektiven Analysen und nutzen quantitative Bildgebungsbiomarker, die aus Computertomographie-Aufnahmen gewonnen wurden.

Die erste Studie konzentriert sich auf die Assoziation zwischen EAT und der Mortalität bei Patienten mit akuter Lungenembolie, wobei festgestellt wurde, dass eine erhöhte EAT-Dichte mit einer höheren 30-Tage-Mortalität verbunden sein könnte, obwohl sich dieser Zusammenhang in der multivariablen Analyse als nicht signifikant erwies.

Die zweite Untersuchung erweitert die Betrachtung von EAT auf Patienten mit COVID-19, wobei hier sowohl eine signifikante Assoziation zwischen der Dichte des EAT und der 30-Tage-Mortalität als auch zwischen EAT-Dichte und der Aufnahme in die Intensivstation festgestellt wurde.

In der dritten Studie wird der Fokus auf die Rolle von SAT und Myosteatose nach allo-HSCT gelegt, wobei niedrige SAT-Werte und Myosteatose mit einer verringerten Gesamtüberlebensrate assoziiert waren. Diese Assoziationen blieben auch nach Anpassung für relevante Kovariaten signifikant. Zusammenfassend deuten unsere Ergebnisse darauf hin, dass die Quantifizierung von Fettgewebe, sowohl EAT als auch SAT, mittels Bildgebung wertvolle prognostische Informationen in verschiedenen klinischen Kontexten liefern kann.

Schlüsselwörter: Epikardiales Fettgewebe, subkutanes Fettgewebe, Computertomographie, Mortalität, allogene hämatopoetische Stammzelltransplantation.

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1. Abkürzungsverzeichnis

ALL ..... *akute lymphatische Leukämie*
allo-HSCT ..... *allogene hämatopoetische Stammzelltransplantation*
BMI ..... *Body-Mass-Index*
cm ..... *Zentimeter*
COVID-19 ..... *Coronavirus-Krankheit-2019*
CT ..... *Computertomographie*
CTCAE ..... *Common Terminology Criteria for Adverse Events*
CTPA ..... Computertomografie der Pulmonalarterien
EAT ..... *epikardiales Fettgewebe*
HR ..... *hazard ratio*
HU ..... *Hounsfield-Einheit*
ICU ..... *Intensive care unit*
IMAT ..... *intramuskuläres Fettgewebe*
IQR ..... *Interquartilsabstand*
KI ..... Konfidenzintervall
kV ..... *Kilovolt*
MDS ..... *myelodysplastisches Syndrom*
MPN ..... *myeloproliferative Neoplasie*
ORs ..... *odds ratio*
OS ..... *Gesamtüberleben*
PE ..... *akute Lungenembolie*
SAT ..... *subkutanes Fettgewebe*
SD ..... *Standardabweichung*
SMI ..... *Skelettmuskelindex*
SM-RA ..... *skeletal muscle radiation attenuation*
SMT ..... *Skelettmuskelgewebe*
SPSS ..... *Statistical Product and Service Solutions*
VAT ..... *viszerales Fettgewebe*
VSR ..... *visceral-to-subcutaneous fat ratio*

2. Einführung

Die vorliegende Dissertation beschäftigt sich mit der prognostischen Relevanz des epikardialen Fettgewebes (EAT) und weiterer Parameter der Körperzusammensetzung im Kontext von drei signifikanten klinischen Herausforderungen: akute Lungenembolie, COVID-19 und die Folgezustände nach allogener hämatopoetischer Stammzelltransplantation (allo-HSCT).

Akute Lungenembolie ist eine Form der venösen Thromboembolie, die potenziell lebensbedrohlich ist und ohne adäquate Behandlung zu signifikant erhöhter Morbidität und Mortalität führen kann (1,2). Die Erkrankung zeichnet sich durch eine plötzliche Blockade der Lungenarterien durch Blutgerinnsel aus. Die Mortalitätsraten variieren stark basierend auf dem initialen klinischen Erscheinungsbild und der Schwere der Symptome, was eine unmittelbare und präzise Risikostratifizierung erfordert (3).

Die COVID-19-Pandemie, verursacht durch das SARS-CoV-2-Virus, hat seit ihrem Ausbruch Anfang 2020 weltweit zu einer beispiellosen gesundheitlichen Krise geführt. Die Krankheit präsentiert sich mit einem breiten Spektrum an klinischen Manifestationen, von milden respiratorischen Symptomen bis hin zu schweren und lebensbedrohlichen Verläufen, einschließlich akuter respiratorischer Distress-Syndrome und multiorganischem Versagen, was die Identifikation prognostischer Marker für schwere Verläufe essenziell macht (4–7).

Die allogene hämatopoetische Stammzelltransplantation ist eine kurative Therapieoption für eine Vielzahl von hämatologischen Malignitäten, einschließlich Leukämien und myelodysplastischen Syndromen (8–11). Trotz ihres Potenzials zur Heilung ist die allo-HSCT mit einem Risiko unmittelbarer und langfristiger Komplikationen verbunden, welche die Lebensqualität beeinträchtigen und die Lebenserwartung verkürzen können (12,13). In diesem Kontext ist die Untersuchung der Körperzusammensetzung von besonderem Interesse, da sie wichtige prognostische Informationen über das Überleben und das Risiko für nachfolgende Komplikationen liefern kann.

Diese Dissertation zielt darauf ab, ein tieferes Verständnis der prognostischen Bedeutung von EAT und anderen Körperkompositionsparametern über diese

Krankheitsspektren hinweg zu erlangen und ihren potenziellen Einfluss auf die Behandlung und Betreuung der betroffenen Patienten zu beleuchten.

2.1 Übersicht über das epikardiale und subkutane Fettgewebe

Epikardiales Fettgewebe (EAT) und subkutanes Fettgewebe (SAT) sind zwei zentrale Fettdepots im menschlichen Körper, die sich sowohl in ihrer Lokalisation als auch in ihrer Funktion unterscheiden und eine wichtige Rolle für die Gesundheit und ergo bei Krankheit spielen (14–19).

EAT ist ein viszerales Fettdepot, das direkt auf der Oberfläche des Herzens zwischen dem Myokard und dem viszeralen Blatt des Perikards liegt (14,15). Es ist metabolisch hochaktiv und produziert eine Reihe von bioaktiven Substanzen, darunter Adipokine und Zytokine, die sowohl parakrine als auch systemische Effekte haben können (15,19). EAT ist besonders wegen seiner engen anatomischen und funktionellen Beziehung zum Herzen von Interesse, da es potenziell die Entwicklung von kardiovaskulären Erkrankungen durch direkte Einflüsse auf das Herz und die angrenzenden Koronargefäße beeinflussen kann.

Im Gegensatz zu EAT befindet sich SAT direkt unter der Haut und ist über den ganzen Körper verteilt. Es dient als größter Energiespeicher des Körpers und spielt eine wichtige Rolle bei der Thermoregulation und dem Schutz der inneren Organe. SAT ist ebenfalls metabolisch aktiv und kann verschiedene bioaktive Substanzen sezernieren, die metabolische und entzündliche Prozesse im Körper beeinflussen. Untersuchungen haben gezeigt, dass die Menge und Verteilung von SAT mit dem Risiko metabolischer Erkrankungen wie Typ-2-Diabetes und Adipositas korreliert (20).

Beide Fettdepots sind somit nicht nur passive Energiespeicher, sondern aktive endokrine Organe, die eine wichtige Rolle in der Regulation des Stoffwechsels und der Entzündungsreaktionen spielen. Ihre Untersuchung bietet potenziell wertvolle Einblicke in die Mechanismen von Krankheiten und könnte zur Entwicklung neuer diagnostischer und therapeutischer Strategien beitragen. Die spezifischen Eigenschaften und Funktionen von EAT und SAT, insbesondere ihre unterschiedlichen Rollen bei verschiedenen Krankheitsbildern, sind ein aktives Forschungsgebiet, das zunehmend an Bedeutung gewinnt.

2.2 Zielsetzung der Studien

Die vorliegende kumulative Arbeit umfasst drei Publikationen, die sich mit der Bewertung von Körperkomposition und Fettverteilung mittels computertomographischer Analysen befassen, um deren Assoziation mit klinischen Ergebnissen in verschiedenen Patientenkollektiven zu untersuchen. Die Zielsetzung jeder Studie wird im Folgenden detailliert beschrieben:

Publikation 1: Analyse des epikardialen Fettgewebes (EAT) bei Patienten mit akuter Lungenembolie

Das primäre Ziel dieser Studie war es, das Volumen und die Dichte des epikardialen Fettgewebes bei Patienten mit akuter Lungenembolie zu messen und zu bewerten, wie diese Parameter mit dem Risiko einer 30-Tage-Mortalität assoziiert sind. Durch den Einsatz spezialisierter Bildgebungssoftware und quantitativer Analysemethoden strebte die Studie an, ein tieferes Verständnis der Rolle des EAT als potenzieller prognostischer Biomarker für akute Lungenembolie zu gewinnen.

Publikation 2: Untersuchung des Zusammenhangs zwischen EAT und klinischen Merkmalen bei COVID-19-Patienten

Diese Studie zielte darauf ab, die Beziehung zwischen dem epikardialen Fettgewebe und verschiedenen klinischen Merkmalen bei Patienten, die mit COVID-19 diagnostiziert wurden, zu erforschen. Insbesondere wurde untersucht, ob und inwiefern das EAT-Volumen und die EAT-Dichte mit dem Schweregrad der Erkrankung und der 30-Tage-Mortalität korrelieren. Durch die Identifizierung von Zusammenhängen zwischen EAT-Parametern und dem klinischen Verlauf von COVID-19 soll ein Beitrag zur Verbesserung der Risikobewertung und zum Management von COVID-19-Patienten geleistet werden.

Publikation 3: Bewertung der Körperkomposition und des Risikos posttransplantationsbedingter Komplikationen nach allogener hämatopoetischer Stammzelltransplantation (allo-HSCT)

Das Hauptziel dieser Studie war es, die Körperkomposition von Patienten vor einer allogenen hämatopoetischen Stammzelltransplantation zu analysieren und wie diese die Wahrscheinlichkeit von frühen posttransplantationsbedingten Nebenwirkungen und das Gesamtüberleben beeinflusst. Durch die Analyse von subkutanem, viszeralem und intermuskulärem Fettgewebe sowie von Skelettmuskelgewebe mittels CT wurde versucht, präzise Biomarker zu identifizieren, die zur Vorhersage von Transplantationserfolg und langfristigen Patientenergebnissen dienen können.

Insgesamt beabsichtigen diese Studien, die Bedeutung der Körperkomposition und spezifischer Fettgewebedepots als prognostische Faktoren in der klinischen Praxis zu unterstreichen und mögliche therapeutische Ansätze aufzuzeigen, die zur Verbesserung der Patientenversorgung und -behandlung beitragen könnten.

3. Material und Methoden

Diese retrospektive kumulative Dissertation wurde gemäß den ethischen Standards des institutionellen und/oder nationalen Forschungskomitees und in Übereinstimmung mit der Helsinki-Deklaration von 1964 und deren späteren Änderungen oder vergleichbaren ethischen Standards durchgeführt. Die Untersuchungen erhielten die Genehmigung der Ethikkommission der Otto-von-Guericke-Universität Magdeburg, Deutschland (Nr. 145/21). Die Notwendigkeit der Einholung einer informierten Zustimmung wurde für alle Studien von der Ethikkommission ausgesetzt.

3.2 Patientenakquise und Auswahlkriterien

Insgesamt wurden 513 Patienten mit akuter Lungenembolie (PE), diagnostizierten COVID-19-Fällen zwischen 2020 und 2022 (237 Patienten) sowie Patienten (122 Patienten), die ihre erste allo-HSCT für bestätigte Leukämie, MDS oder MPN zwischen Januar 2015 und Oktober 2021 erhalten haben, retrospektiv bewertet. Die Patientenauswahl erfolgte aus der internen klinischen Datenbank (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Deutschland), wobei folgende Einschlusskriterien angewandt wurden:

- für PE-Patienten: ausreichende CT-Bilder mit deutlich sichtbarer PE bei der Aufnahme ins Krankenhaus und verfügbare klinische Daten zu klinischen Anzeichen, serologischen Parametern und Nachverfolgung
- für COVID-19-Patienten: CT-Bildgebung zum Zeitpunkt der Aufnahme ins Krankenhaus, klinische Daten zum Ergebnis, PCR-bewiesene COVID-19-Infektion
- für allo-HSCT-Patienten: Patienten (≥ 18 Jahre alt), die ihre erste allo-HSCT für bestätigte Leukämie, MDS oder MPN erhalten haben, mit CT des Brustkorbs, des Abdomens und des Beckens, durchgeführt innerhalb von vier Wochen vor der allo-HSCT

Ausschlusskriterien waren schwere Bildartefakte, fehlende klinische Daten/Nachverfolgung, Thrombolyse vor der CT-Bildgebung und chronische PE.

3.3 CT-basierte Messung des epikardialen, subkutanen und viszeralen Fettgewebes

In der vorliegenden kumulativen Doktorarbeit wurden die Volumina und Dichten des epikardialen, subkutanen und viszeralen Fettgewebes mittels computertomographischer Verfahren analysiert, um deren potenzielle Rolle als Biomarker für kardiovaskuläre Erkrankungen und andere metabolische Pathologien zu untersuchen. Die Messung des EAT erfolgte in zwei der Studien mit identischen Methoden, während die dritte Studie sich auf die Analyse des Fettgewebes (SAT und VAT) sowie des Skelettmuskelgewebes (SMT) und des intermuskulären Fettgewebes (IMAT) konzentrierte.

Messung des epikardialen Fettgewebes

In den ersten beiden Studien führte ein geschulter Radiologe (Autor der Dissertation), der keine Kenntnisse über Patientenergebnisse hatte, die Messung des EAT-Volumens durch. Die Messungen wurden mit einer spezialisierten Workstation unter Verwendung von Intellispace Portal (Version 11; Philips, Amsterdam, Niederlande) durchgeführt. Das EAT-Volumen wurde berechnet, indem Dichtewerte im Bereich zwischen -30 und -190 Hounsfield-Einheiten (HU) für Fettgewebe berücksichtigt wurden. Als anatomische Grenzen dienten die Bifurkation der Pulmonalarterie, der linke Vorhof und die Aortenwurzel als obere Grenze sowie das Zwerchfell und der Apex des linken Ventrikels als untere Grenze. Zusätzlich wurde die mittlere Dichte in HU berechnet. Die Berechnungen basierten auf in der Literatur zuvor beschriebenen Methoden (21-25).

Messung des subkutanen und viszeralen Fettgewebes sowie des Skelettmuskelgewebes

In der dritten Studie wurden CT-Scans mit einem Canon Aquilion Prime (Canon Medical Systems, Otawara, Japan) oder einem Siemens SOMATOM Definition AS+ (Siemens Healthcare, Erlangen, Deutschland) Multidetektor-CT-Scanner durchgeführt. Die Patienten wurden in Rückenlage gescannt, unter Verwendung eines Protokolls, das 1 mm dicke Akquisitionsschichten mit 5 mm Rekonstruktionen, eine Röhrenspannung von 120 kV, automatische Röhrenstrommodulation, einen Pitchfaktor von 1,2 und eine Kollimation von 0,6 mm umfasste. Die Segmentierungstechnik wählte Serien mit einer axialen Schichtdicke von 5 mm und

einem Weichgewebskern auf der Höhe der dritten Lendenwirbelsäule (L3). Die Querschnittsflächen des SMT, SAT, VAT und IMAT wurden semi-automatisch mit der Software ImageJ 1.48v (Wayne Rasband, National Institutes of Health, Maryland, USA) gemessen. Zudem wurde die mittlere SM-RA als Indikator für Muskelqualität und Myosteatosis in HU festgehalten.

Die Ergebnisse dieser Studien tragen wesentlich zum Verständnis der komplexen Rolle bei, die das Fettgewebe und die Körperkomposition bei der Entwicklung und dem Verlauf verschiedener Krankheitsbilder spielen. Die einheitliche Anwendung präziser und validierter Messmethoden ermöglicht eine genaue Quantifizierung dieser Gewebetypen und bietet eine solide Grundlage für zukünftige Forschungen in diesem Bereich.

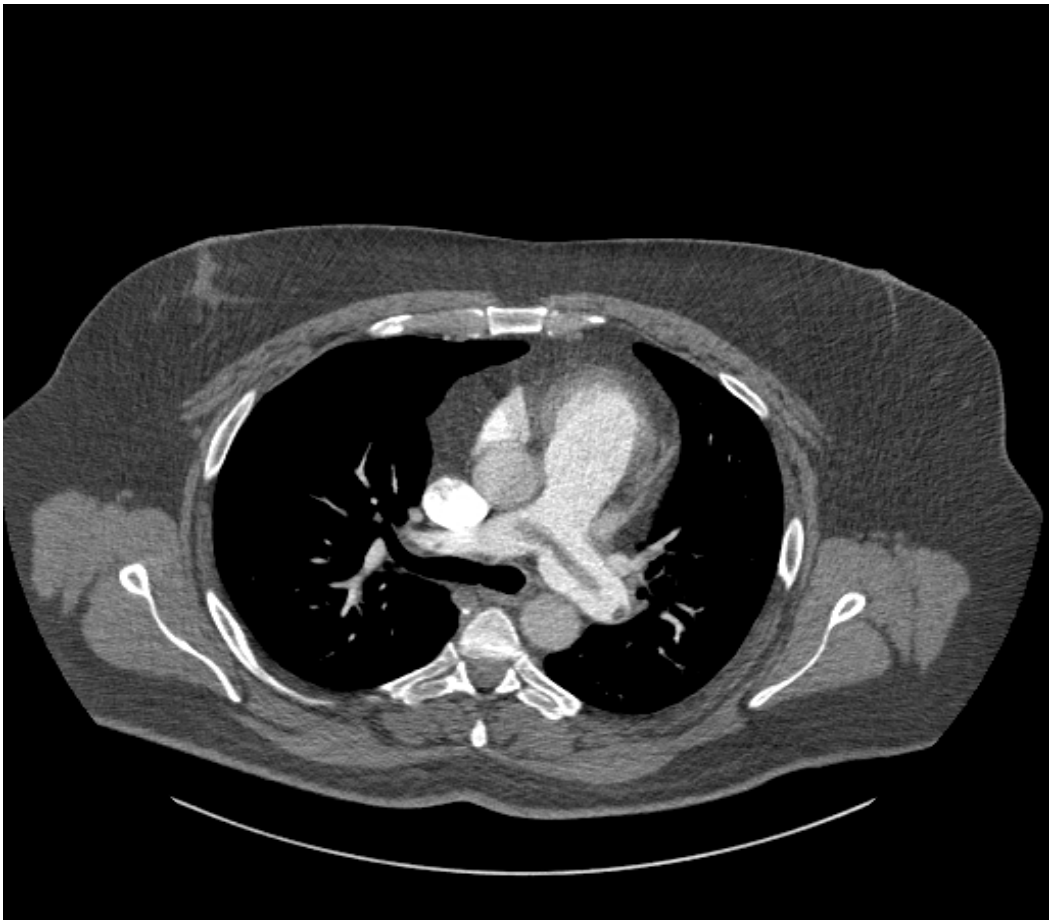

***Abbildung 1**.: repräsentativer Fall der Patientenprobe, CTPA mit zentraler akuter PE (axiale Schichtführung). Das EAT-Volumen beträgt 415,2 cm³ und die mittlere Dichte beträgt -82,7 HU.*

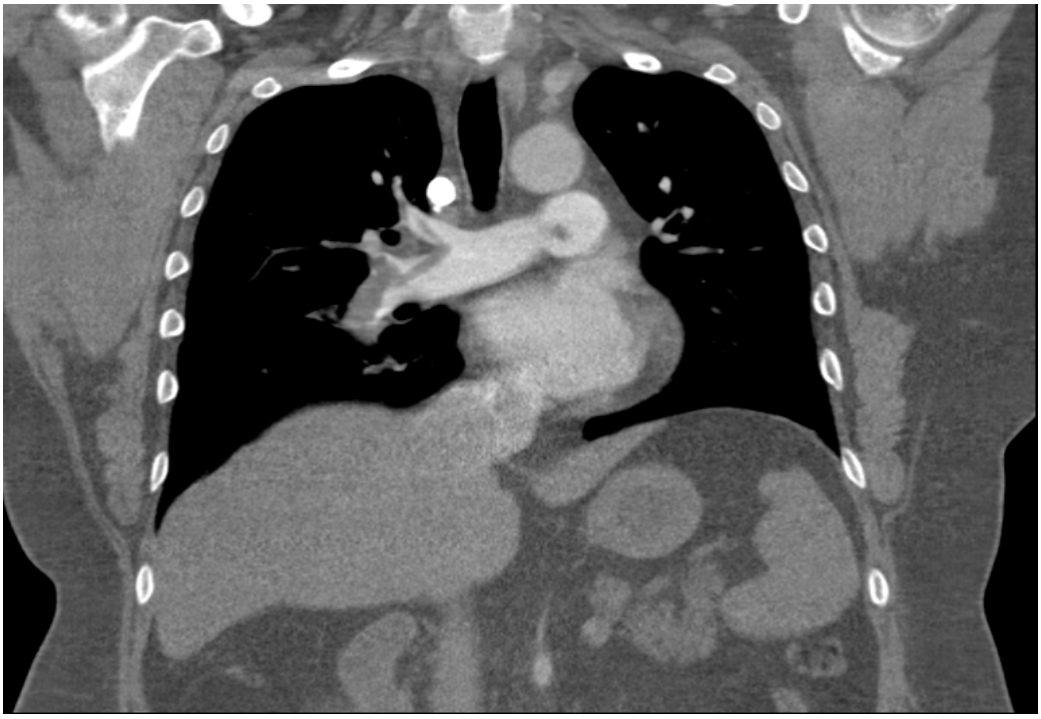

Abbildung 2.: *repräsentativer Fall der Patientenprobe, CTPA mit zentraler akuter PE (coronare Schichtführung). Das EAT-Volumen beträgt 415,2 cm³ und die mittlere Dichte beträgt -82,7 HU.*

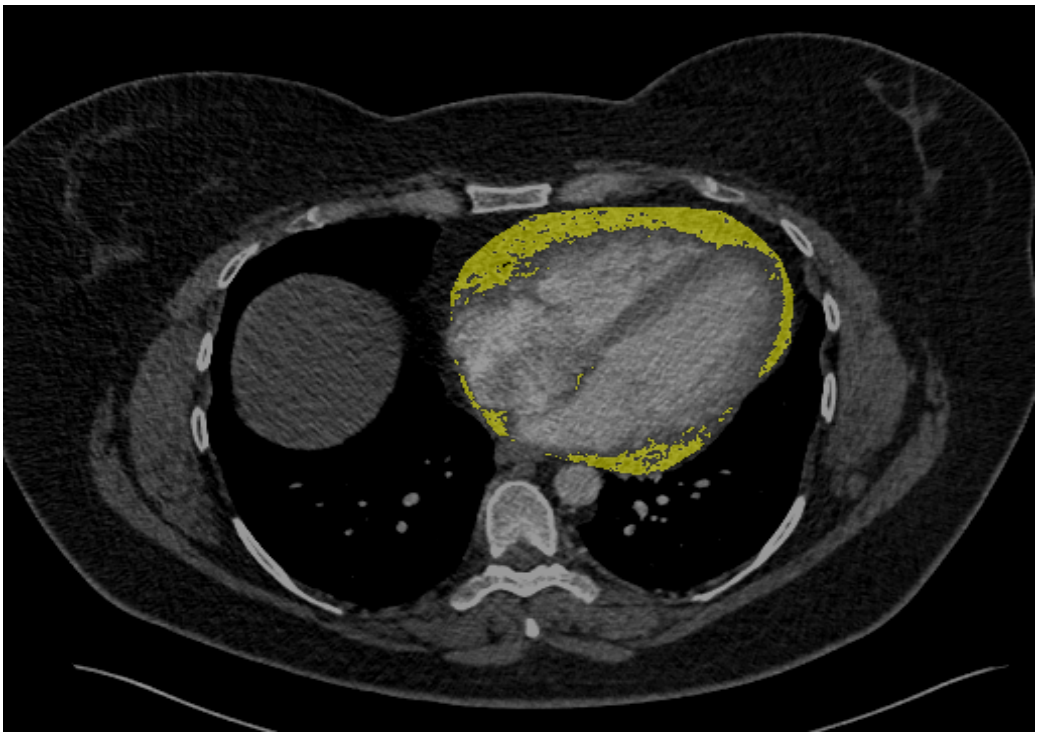

***Abbildung 3**.: repräsentativer Fall der Patientenprobe, CTPA mit zentraler akuter PE. Die EAT-Segmentierung wird durch ein gelbes Overlay visualisiert. Das EAT-Volumen beträgt 415,2 cm³ und die mittlere Dichte beträgt -82,7 HU.*

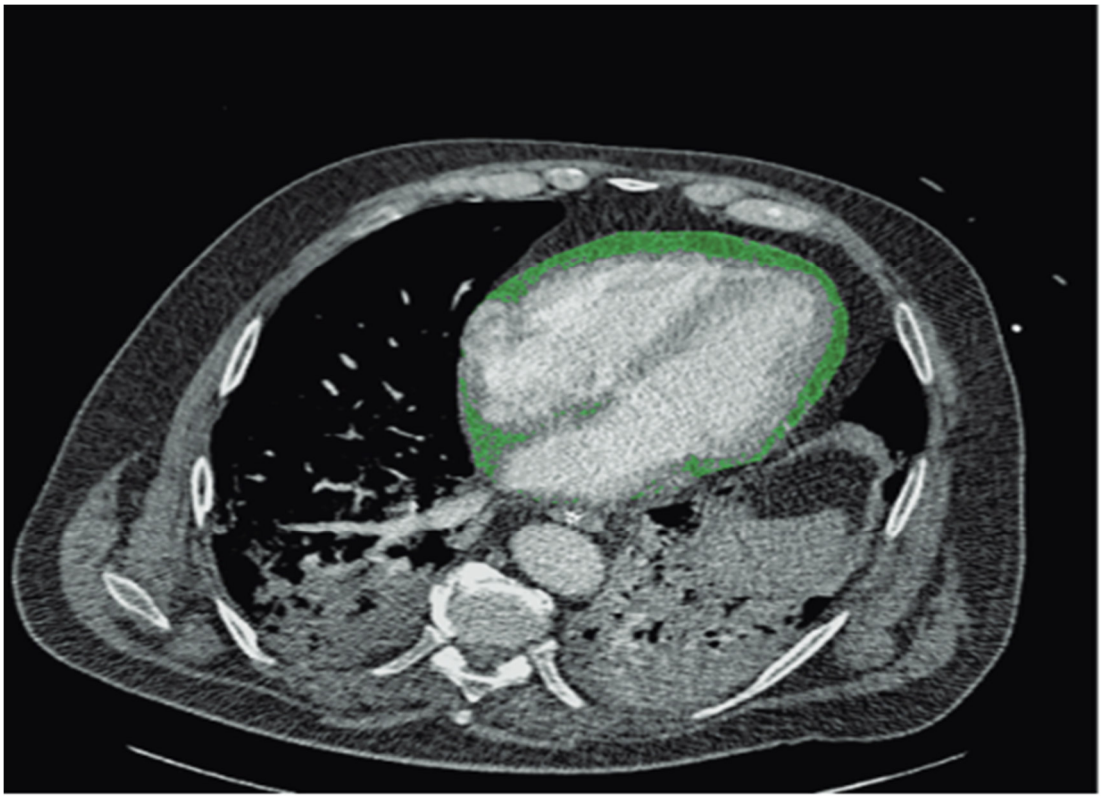

Abbildung 4.: *ein repräsentativer Fall aus der Patientenstichprobe mit COVID-19. Die Segmentierung des EAT wird mit einem grünen Overlay visualisiert. Das resultierende EAT-Volumen beträgt 40,9 cm³ und die Dichte -79,9 HU.*

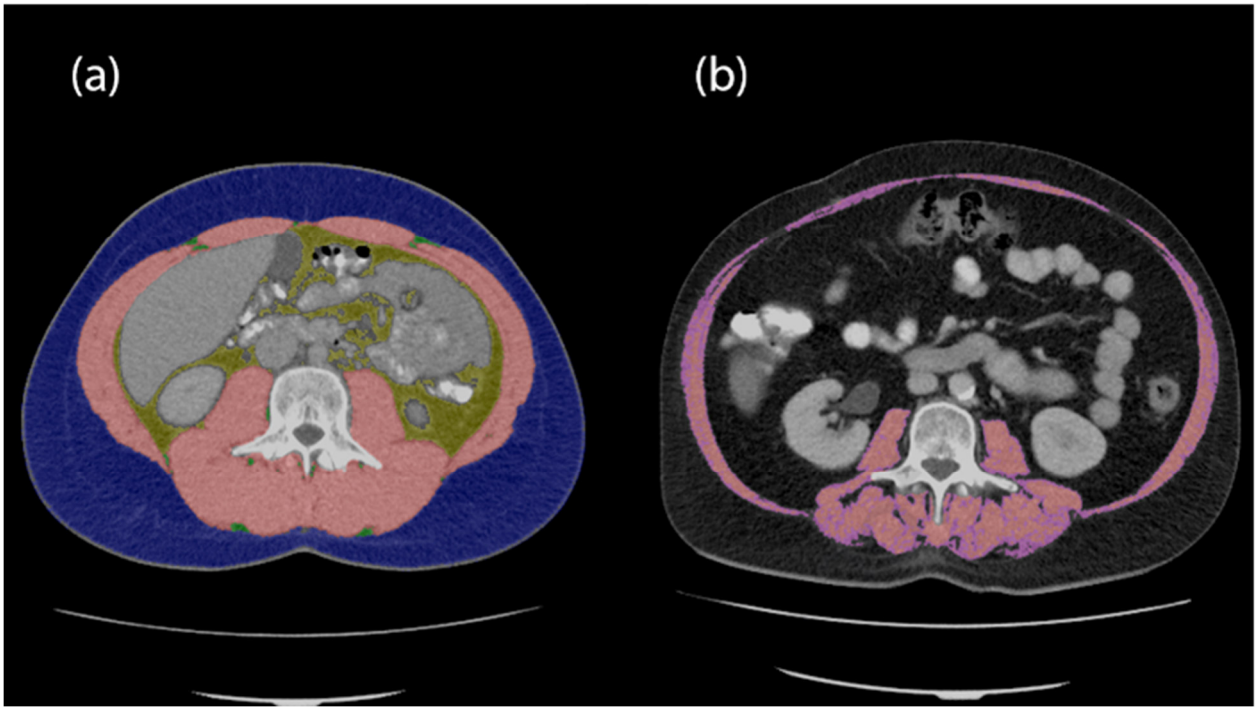

Abbildung 5.: *CT-ermittelte Körperzusammensetzung auf Höhe des dritten Lendenwirbels (L3): (a) blau, SAT; rosa, SMT; grün, IMAT; und gelb, VAT. (b) lila, SM-RA (-30 bis 30 HU).*

3.4 Statistische Auswertung

Im Rahmen dieser kumulativen Arbeit wurde die statistische Analyse unter Einsatz von SPSS (IBM SPSS Statistics für Windows, Version 225.0, IBM Corp., Armonk, NY, USA) durchgeführt. Zur grafischen Darstellung der Ergebnisse kam GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA) zum Einsatz. Die erhobenen Daten wurden zunächst mittels deskriptiver Statistik ausgewertet, wobei absolute und relative Häufigkeiten zur Anwendung kamen. Gruppenunterschiede wurden, sofern angebracht, mit dem Mann-Whitney-U-Test und dem exaktem Fisher -Test berechnet. Zur Aufdeckung von Zusammenhängen zwischen den Parametern wurden Korrelationsanalysen unter Verwendung des Spearman-Korrelationskoeffizienten durchgeführt. Sowohl uni- als auch multivariable logistische Regressionsanalysen kamen zur Untersuchung der Assoziationen mit der 30-Tage-Mortalität zum Einsatz. In allen Fällen deutete ein p-Wert < 0,05 auf statistische Signifikanz hin.

Die Normalverteilung der Daten wurde mit dem Kolmogorov-Smirnov-Test geprüft. Deskriptive Statistiken wurden als Median und Interquartilsabstand (IQR) für Daten mit nicht-parametrischer Verteilung und als Mittelwert und Standardabweichung (SD) für parametrische Verteilungen präsentiert. Die Korrelation zwischen dem Body-Mass-Index (BMI) und den Körperkompositionsparametern wurde mittels Spearman-Rangkorrelationskoeffizienten berechnet. Univariate und multivariate Cox-Regressionsanalysen wurden verwendet, um die Assoziation der Körperkompositionsparameter (basierend auf dichotomen Merkmalen) mit dem Gesamtüberleben (OS) zu bewerten. Cox-Regressionsmodelle, angepasst für relevante Kovariaten wie Alter, Geschlecht, Graft-versus-Host-Disease, Organversagen, Nierenversagen, posttransplantationsbedingte Nebenwirkungen und schwere Nebenwirkungen gemäß CTCAE (≥ Grad 4), wurden ebenfalls zur Überprüfung der Assoziation genutzt. Hazard Ratios (HRs) werden zusammen mit 95% Konfidenzintervallen (KI) präsentiert. Die Kaplan-Meier-Methode kam zur Schätzung der Überlebenswahrscheinlichkeiten zum Einsatz, die zwischen den Gruppen der Körperkomposition unter Verwendung des Log-Rank-Tests verglichen wurden. Zusätzlich wurde ein binäres logistisches Regressionsmodell (unangepasst und angepasst für Alter und Geschlecht) durchgeführt, um die Assoziation zwischen den Körperkompositionsgruppen als Risikofaktoren für spezifische frühe posttransplantationsbedingte unerwünschte Ereignisse gemäß CTCAE (Grad 3 oder ≥

4) zu untersuchen. Odds Ratios (ORs) werden zusammen mit 95 % KI präsentiert. Ein zweiseitiger p-Wert ≤ 0,05 wurde als statistisch signifikant betrachtet. Diese statistischen Methoden ermöglichten eine umfassende Auswertung der Zusammenhänge zwischen verschiedenen Körperkompositionsparametern und klinischen Ausgängen. Die Ergebnisse tragen somit zur Erweiterung des Verständnisses bei, wie Körperkomposition als potenzieller Biomarker für prognostische Bewertungen in der medizinischen Forschung sowie in der Therapie und Diagnostik genutzt werden kann.

4. Eigene Arbeiten

4.1. Originalarbeit 1

Epicardial adipose tissue as a prognostic marker in acute pulmonary embolism

Aghayev A, Hinnerichs M, Wienke A, Meyer HJ, Surov A.

Das epikardiale Fettgewebe (EAT) hat sich als quantitativer Bildgebungsmarker etabliert, der mit der Krankheitsschwere bei koronarer Herzkrankheit assoziiert ist (14,15). Unser Ziel war es, diesen prognostischen Marker, der aus der computertomographischen Pulmonalisangiographie (CTPA) abgeleitet wurde, zur Vorhersage von Mortalität bei Patienten mit akuter Lungenembolie zu nutzen.

Die klinische Datenbank wurde retrospektiv nach Patienten mit akuter Lungenembolie zwischen 2015 und 2021 durchsucht. Insgesamt wurden 513 Patienten (216 weiblich, 42,1 %) in die Analyse einbezogen. Der Studienendpunkt war die 30-Tage-Mortalität. Das epikardiale Fettgewebe wurde auf der diagnostischen CTPA auf semiquantitative Weise gemessen. Das Volumen und die Dichte des EAT wurden für jeden Patienten ermittelt.

Insgesamt starben 60 Patienten (10,4 %) innerhalb des 30-tägigen Beobachtungszeitraums. Das durchschnittliche EAT-Volumen betrug bei Überlebenden 128,3 ± 65,0 cm^3 und bei Nichtüberlebenden 154,6 ± 84,5 cm^3 ($p = 0,02$). Die Dichte des EAT lag bei Überlebenden bei -79,4 ± 8,3 HU und bei Nichtüberlebenden bei -76,0 ± 8,4 HU ($p = 0,86$), und die EAT-Dichte war mit der 30-Tage-Mortalität assoziiert (OR = 1,07; 95 % KI [1,03; 1,1]; $p < 0,001$), blieb jedoch in der multivariablen Analyse nicht statistisch signifikant. Es wurde keine Assoziation zwischen dem EAT-Volumen und der 30-Tage-Mortalität identifiziert (OR = 1,0; 95 % KI [1,0; 1,0]; $p = 0,48$)

Schlussfolgerung: Es könnte eine Assoziation zwischen der EAT-Dichte und der Mortalität bei Patienten mit akuter Lungenembolie bestehen. Weitere Studien sind erforderlich, um die prognostische Relevanz der EAT-Parameter bei Patienten mit akuter Lungenembolie zu klären.

4.2. Originalarbeit 2

Epicardial Adipose Tissue as a Prognostic Marker in COVID-19

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Das epikardiale Fettgewebe (EAT) hat sich als quantitativer Bildgebungsmarker etabliert, der mit der Prognose verschiedener Krankheiten, insbesondere kardiovaskulärer Erkrankungen, assoziiert ist (14,15). Der kardiale Schaden durch die Coronavirus-Krankheit 2019 (COVID-19) könnte mit dem EAT in Verbindung stehen (26-28). Diese Studie zielte darauf ab, diesen prognostischen Marker, der aus Computertomographie (CT)-Bildern abgeleitet wurde, zur Vorhersage der 30-Tage-Mortalität bei Patienten mit COVID-19 zu nutzen.

Konsekutive Patienten mit COVID-19 wurden zwischen 2020 und 2022 retrospektiv erfasst. Insgesamt wurden 237 Patienten (78 weiblich, 32,9 %) in die vorliegende Studie einbezogen. Der Studienendpunkt war die 30-Tage-Mortalität. Das EAT wurde mit der diagnostischen CT auf semiquantitative Weise gemessen. EAT-Volumen und -Dichte wurden für jeden Patienten ermittelt.

Insgesamt starben 70 Patienten (29,5 %) innerhalb des 30-tägigen Beobachtungszeitraums, und 143 Patienten (60,3 %) wurden auf die Intensivstation (ICU) aufgenommen. Das durchschnittliche EAT-Volumen betrug bei Überlebenden 140,9 ± 89,1 cm^3 und bei Nichtüberlebenden 132,9 ± 77,7 cm^3, $p = 0,66$. Die durchschnittliche EAT-Dichte lag bei Überlebenden bei -71,9 ± 8,1 Hounsfield-Einheiten (HU) und bei Nichtüberlebenden bei -67,3 ± 8,4 HU, $p = 0,0001$ (Tabelle 4, Abbildung 8). Die EAT-Dichte war mit der 30-Tage-Mortalität ($p < 0,0001$) und der Aufnahme auf die ICU ($p<0,0001$) assoziiert. Das EAT-Volumen war nicht mit Mortalität und/oder ICU-Aufnahme assoziiert.

Schlussfolgerung: Die EAT-Dichte war mit der 30-Tage-Mortalität und der ICU-Aufnahme bei Patienten mit COVID-19 assoziiert.

4.3. Originalarbeit 3

Low subcutaneous adipose tissue and myosteatosis are prognostic factors after allogeneic hematopoietic stem cell transplantation

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Die allogene hämatopoetische Stammzelltransplantation (allo-HSCT) stellt die einzige kurative Behandlungsoption für verschiedene hämatologische Neoplasien dar (12,13). Diese Studie zielte darauf ab, die Parameter der Körperkomposition als Prädiktoren für das Gesamtüberleben (OS) nach der Transplantation und unerwünschte Ereignisse bei Patienten mit Leukämie, myelodysplastischen Syndromen (MDS) und myeloproliferativen Neoplasien (MPN) zu bewerten.

Es handelte sich um eine retrospektive Studie mit 122 erwachsenen Patienten, die ihre erste allo-HSCT erhielten. Die CT-basierte halbautomatisierte Messung von subkutanem Fettgewebe (SAT), viszeralem Fettgewebe (VAT), viszeralem zu subkutanem Fettverhältnis (VSR), Sarkopenie in Bezug auf den Skelettmuskelindex (SMI) und Myosteatose basierend auf der Strahlenabschwächung des Skelettmuskels (SM-RA) wurde durchgeführt. Die Cox-Regressionsanalyse wurde verwendet, um den Zusammenhang der Körperkompositionsparameter mit dem OS zu bewerten.

In der univariaten Analyse waren ein niedriges SAT und Myosteatose mit einem niedrigeren OS assoziiert (hazard ratio [HR] 2,02; 95 % Konfidenzintervall [KI] [1,16; 3,51]; p = 0,01) bzw. (HR 2,50; 95 % KI [1,48;4,25]; p = < 0,001). Diese Assoziation blieb auch nach Anpassung für relevante Kovariaten signifikant, mit HR 2,32; 95 % KI [1,23; 4,38]; p = 0,01 und HR 2,86; 95 % KI [1,51; 5,43]; p = < 0,001. Im Gegensatz dazu waren VAT, VSR, Sarkopenie und sarkopenische Adipositas in Bezug auf OS nicht statistisch signifikant. Schwere posttransplantationsbedingte Nebenwirkungen traten häufiger in der Gruppe mit niedrigem SAT auf (odds ratio [OR] 3,12; 95 % KI [1,32; 7,40]; p = 0,01) und OR 3,17; 95 % KI [1,31; 7,70]; p = < 0,01 in der alters- und geschlechtsangepassten Analyse.

Schlussfolgerung: Niedriges SAT und Myosteatose können zu einem erhöhten Sterblichkeitsrisiko beitragen, während niedriges SAT das Risiko für schwere posttransplantationsbedingte Nebenwirkungen zu erhöhen scheint.

5. Diskussion

Die durchgeführten Studien liefern wichtige Einsichten in die prognostische Bedeutung von Körperzusammensetzungsparametern in verschiedenen medizinischen Kontexten. Die differenzierte Analyse verschiedener Fettgewebetypen, einschließlich des epikardialen (EAT) und subkutanen Fettgewebes (SAT), sowie die Bewertung von Myosteatose bieten neue Perspektiven für die Risikostratifizierung und das Management von Patienten mit sowohl akuten als auch chronischen Erkrankungen.

Lungenarterienembolie (LAE) stellt eine bedeutende klinische Herausforderung dar, die ohne prompte Diagnose und Behandlung zu schwerwiegenden Folgen, einschließlich Tod führen kann (3). Als eine der Hauptursachen für kardiovaskuläre Morbidität und Mortalität weltweit, bedarf die LAE einer schnellen Risikostratifizierung, um das Behandlungsregime und die Überwachungsintensität anzupassen (29,30). Die Diagnostik stützt sich auf eine Kombination aus klinischer Bewertung, bildgebenden Verfahren wie Computertomographie der Pulmonalarterien (CTPA) und Ultraschall der unteren Extremitäten, sowie Biomarkern.

Epikardiales Fettgewebe (EAT) hat in jüngster Zeit Aufmerksamkeit als potenzieller Biomarker in der Diagnostik und Prognose der LAE gewonnen. EAT, das Fettgewebe, das das Herz umgibt, spielt eine wichtige Rolle in der kardialen Physiologie, einschließlich der Bereitstellung von Fettsäuren für den Energiestoffwechsel des Herzens, dem Schutz der Koronararterien durch mechanische Polsterung und möglicherweise der Modulation der Entzündungsreaktion im Herzen (6,14).

Die Bedeutung von EAT geht über seine lokalen Effekte hinaus. Studien haben eine Verbindung zwischen der Menge und Dichte des EAT und verschiedenen kardiovaskulären Risikofaktoren, einschließlich Rauchen, Diabetes, Dyslipidämie und anderen Stoffwechselstörungen, aufgezeigt (31). Eine erhöhte EAT-Menge wurde mit einem ungünstigen Lipidprofil, höherem Body-Mass-Index (BMI) und Insulinresistenz in Verbindung gebracht(31). Diese Assoziationen deuten darauf hin, dass EAT nicht nur ein passiver Energiespeicher ist, sondern auch aktiv an der Pathogenese kardiovaskulärer Erkrankungen beteiligt sein könnte.

Insbesondere hat die Forschung einen Zusammenhang zwischen EAT und der linksventrikulären Dysfunktion untersucht, was auf die potenzielle Rolle von EAT in der

Beeinträchtigung der kardialen Funktion hinweist. Die Erhöhung der EAT-Menge und -Dichte könnte eine direkte mechanische Belastung für das Herz darstellen oder durch die Sekretion proinflammatorischer Zytokine indirekt zur Herzschädigung beitragen (32-34).

Im Kontext der akuten Lungenembolie hat die erste Publikation die prognostische Bedeutung der EAT-Dichte hervorgehoben. Es wurde festgestellt, dass eine erhöhte EAT-Dichte mit einer gesteigerten 30-Tage-Mortalität assoziiert ist, was auf die potenzielle Rolle von EAT als Indikator für ein erhöhtes Risiko hinweist. Im Gegensatz dazu zeigte das EAT-Volumen keine direkte Korrelation mit dem kurzfristigen Überleben, was die spezifische Bedeutung der Gewebedichte über das reine Volumen hinaus unterstreicht. Diese Unterscheidung ist kritisch, da sie darauf hinweist, dass die Dichte von EAT, möglicherweise durch die Reflexion des entzündlichen Zustands oder der metabolischen Aktivität des Gewebes, einen direkteren Einblick in das kardiovaskuläre Risiko bietet als das Volumen allein.

Die Ergebnisse unterstreichen die Notwendigkeit, EAT-Dichte als einen neuen Biomarker in der Risikobewertung für Patienten mit akuter Lungenembolie zu berücksichtigen. Durch die Integration von EAT-Dichtemessungen in das diagnostische und prognostische Arsenal könnte die klinische Entscheidungsfindung verbessert werden, indem Patienten, die ein höheres Risiko für adverse Ereignisse tragen, effektiver identifiziert und entsprechend intensiver überwacht und behandelt werden.

Die zweite Publikation fokussiert auf die kritische Rolle der epikardialen Fettgewebedichte (EAT-Dichte) bei Patienten mit COVID-19 und wie diese mit der Prognose der Erkrankung zusammenhängt. Dieser Fokus ist entscheidend, da COVID-19 bekanntermaßen erhebliche kardiale Komplikationen verursachen kann, was die Bedeutung des Verständnisses aller potenziellen kardialen Risikofaktoren, einschließlich der EAT-Dichte, unterstreicht (5).

Die Kernhypothese dieser Studie war, dass eine erhöhte Dichte des EAT bei Patienten mit COVID-19 mit einer schlechteren Prognose verbunden ist, einschließlich höherer Mortalitätsraten und einem erhöhten Bedarf an intensivmedizinischer Versorgung. Diese Hypothese stützt sich auf das wachsende Verständnis der Rolle des EAT in

kardiovaskulären Erkrankungen und wie Entzündungsprozesse im EAT möglicherweise die kardiale Funktion beeinträchtigen können.

Die Ergebnisse bestätigen die Hypothese und zeigen eine signifikante Korrelation zwischen erhöhter EAT-Dichte und negativen COVID-19-Ergebnissen. Diese Assoziation bleibt bestehen, auch nachdem für andere Risikofaktoren kontrolliert wurden, was die spezifische Bedeutung der EAT-Dichte als unabhängiger Risikofaktor hervorhebt. Diese Erkenntnisse sind besonders relevant, da sie auf eine mögliche neue Route hinweisen, durch die COVID-19 kardiale Schäden verursachen kann.

Verglichen mit der bestehenden Literatur ergänzen und erweitern unsere Ergebnisse das Verständnis der komplexen Wechselwirkungen zwischen COVID-19 und dem kardiovaskulären System. Frühere Studien haben die Beziehung zwischen COVID-19 und erhöhtem Risiko für kardiovaskuläre Komplikationen hervorgehoben, jedoch wurde der spezifische Beitrag der EAT-Dichte nicht ausführlich untersucht.(35) Unsere Arbeit bietet daher wertvolle neue Einblicke in die Bedeutung der EAT-Dichte als prognostischer Marker bei COVID-19.

Die dritte Publikation konzentriert sich auf die Auswirkungen der Körperzusammensetzung, insbesondere auf Faktoren wie SAT und Myosteatosis, auf OS nach einer allo-HSCT bei Patienten mit hämatologischen Malignitäten wie Leukämie, MDS und MPN.

Die zentrale Fragestellung dieser Untersuchung war, ob Veränderungen in der Körperzusammensetzung, wie niedriges SAT und das Vorhandensein von Myosteatosis, das Risiko für posttransplantatorische Mortalität und das Auftreten schwerwiegender nachfolgender Komplikationen beeinflussen. In Anbetracht der global steigenden Prävalenz von Übergewicht und Adipositas, die ebenfalls bei Kindern beobachtet wird, die einer allogenen hämatopoetischen Stammzelltransplantation (allo-HSCT) unterzogen werden, erlangt diese Forschungsfrage eine signifikante klinische Relevanz (36).

Die Ergebnisse zeigen, dass niedriges SAT und Myosteatosis signifikant mit einem erhöhten Risiko für posttransplantatorische Mortalität verbunden sind. Diese Befunde unterstreichen die Wichtigkeit der prätransplantatorischen Bewertung der Körperzusammensetzung. Besonders bei Kindern, die aufgrund der Adipositas-

Epidemie zunehmend von Übergewicht betroffen sind, könnte dies von Bedeutung sein, da Veränderungen im Körpergewicht während der Therapie die Vulnerabilität gegenüber schweren Krankheitsverläufen und Therapiekomplikationen erhöhen können.

Diese Studie ergänzt die wachsende Literatur über die Rolle der Körperzusammensetzung in der Onkologie und Transplantationsmedizin. Während frühere Arbeiten den Fokus auf den Einfluss von Übergewicht und Adipositas auf die Therapieergebnisse gelegt haben,(36) bietet unsere Untersuchung spezifische Einblicke in die Bedeutung von SAT und Myosteatosis. Die Ergebnisse stimmen mit Studien überein, die zeigen, dass bei Kindern mit ALL, die Therapien erhalten, Veränderungen in der Körperzusammensetzung, insbesondere ein Anstieg des Fettgewebes, häufig sind und potenziell das Behandlungsergebnis beeinflussen können (36).

Die kombinierte Analyse dieser Studien zeigt die komplexen und vielfältigen Rollen, die Fettgewebe in der Pathophysiologie von Krankheiten und deren Prognose spielt. Es wird deutlich, dass eine umfassende Bewertung von Fettgewebe, einschließlich seiner Verteilung und Qualität, für eine genaue Risikostratifizierung unerlässlich ist. Diese Erkenntnisse fordern eine stärkere Berücksichtigung von Körperzusammensetzungsparametern in klinischen Richtlinien und in der Entwicklung neuer therapeutischer Strategien.

Zukünftige Forschungsarbeiten sollten darauf abzielen, die biologischen Mechanismen zu entschlüsseln, die den beobachteten Assoziationen zugrunde liegen, und die klinische Anwendbarkeit von Fettgewebsparametern in verschiedenen Patientenpopulationen weiter zu validieren. Darüber hinaus ist die Entwicklung von präzisen, nicht-invasiven Methoden zur Messung von Fettgewebsdichte und -verteilung von entscheidender Bedeutung, um die Integration dieser Parameter in die routinemäßige Patientenbewertung zu erleichtern.

Insgesamt bieten die Ergebnisse dieser Forschung wertvolle Einblicke in die prognostische Bedeutung von Fettgewebe und legen den Grundstein für die Entwicklung personalisierter Behandlungsansätze, die auf einer detaillierten Bewertung der Körperzusammensetzung basieren. Die Berücksichtigung dieser

Parameter könnte zu einer verbesserten Patientenversorgung und besseren klinischen Ergebnissen führen.

5.1. Limitationen

Originalarbeit 1

Die Hauptlimitation der ersten Publikation liegt in der begrenzten Stichprobengröße und dem retrospektiven Studiendesign, was die Generalisierbarkeit der Ergebnisse einschränken könnte. Zudem war die EAT-Segmentierung manuell, was zeitaufwendig ist und zu potenziellen Messabweichungen führen könnte.

Originalarbeit 2

Die zweite Publikation leidet unter ähnlichen Einschränkungen wie die erste, einschließlich einer begrenzten Patientenpopulation und der retrospektiven Natur der Analyse. Darüber hinaus könnten die unterschiedlichen Wellen der Pandemie und deren variierende klinische Schwere die Ergebnisse beeinflusst haben, was in der Studie nicht vollständig angepasst wurde.

Originalarbeit 3

Die dritte Studie umfasste eine heterogene Gruppe von hämatologischen Malignitäten, was die Analyseergebnisse verzerren könnte. Zudem war die Studie monozentrisch und retrospektiv, was die Übertragbarkeit der Ergebnisse auf andere klinische Settings begrenzt. Weiterhin wurde die Rolle von Komorbiditäten und vorherigen Behandlungen nicht untersucht, was wichtige Störfaktoren sein könnten.

6. Zusammenfassung

Diese kumulative Arbeit untersucht die Rolle des epikardialen Fettgewebes (EAT) und des viszeralen sowie subkutanen Fettgewebes (VAT bzw. SAT) in Bezug auf die Prognose bei akuter Lungenembolie, COVID-19, und nach allogener hämatopoetischer Stammzelltransplantation (allo-HSCT) bei hämatologischen Malignomen. Die Forschungsarbeiten offenbaren, wie quantifizierte Bildgebungsbefunde des Fettgewebes entscheidende prognostische Informationen in unterschiedlichen klinischen Szenarien liefern können.

Bei akuter Lungenembolie zeigt sich, dass insbesondere die Dichte des EAT, nicht jedoch dessen Volumen, mit der 30-Tage-Mortalität assoziiert ist. Diese Erkenntnis legt nahe, dass die qualitative Bewertung des EAT wichtige prognostische Hinweise liefern könnte, welche in zukünftigen Studien weiter erforscht werden sollten.

Im Kontext von COVID-19 wird ebenfalls die prognostische Relevanz des EAT untersucht. Ähnlich wie bei der Lungenembolie wird die Bedeutung der EAT-Dichte hervorgehoben. Diese Ergebnisse stützen die Annahme, dass EAT als Biomarker für die Risikostratifizierung bei COVID-19-Patienten dienen könnte.

Die dritte Studie fokussiert auf die Bedeutung von viszeralem und subkutanem Fettgewebe nach allo-HSCT bei Patienten mit Leukämie, MDS und MPN. Es wird deutlich, dass ein niedriges subkutanes Fettgewebe und Myosteatose mit einem erhöhten Risiko für Mortalität verbunden sind, was die Notwendigkeit einer prätransplantativen Bewertung der Körperzusammensetzung unterstreicht.

Zusammenfassend verdeutlichen diese Arbeiten die komplexe und vielfältige Rolle von Fettgewebe in der Krankheitsprognose. Die Integration von Fettgewebsparametern in die klinische Praxis könnte eine präzisere Risikostratifizierung ermöglichen und zur Entwicklung personalisierter Behandlungsansätze beitragen. Zukünftige Forschung sollte darauf abzielen, die biologischen Mechanismen zu entschlüsseln, die den beobachteten Assoziationen zugrunde liegen, und die klinische Anwendbarkeit dieser Biomarker in verschiedenen Patientenpopulationen weiter zu validieren.

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Epicardial adipose tissue as a prognostic marker in acute pulmonary embolism

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Abstract

Background: Epicardial adipose tissue (EAT) has been established as a quantitative imaging biomarker associated with disease severity in coronary heart disease. Our aim was to use this prognostic marker derived from computed tomography pulmonary angiography (CTPA) for the prediction of mortality and prognosis in patients with acute pulmonary embolism.
Methods: The clinical database was retrospectively screened for patients with acute pulmonary embolism between 2015 and 2021. Overall, 513 patients (216 female, 42.1%) were included in the analysis. The study end-point was 30-day mortality. Epicardial adipose tissue was measured on the diagnostic CTPA in a semiquantitative manner. The volume and density of EAT were measured for every patient.
Results: Overall, 60 patients (10.4%) died within the 30-day observation period. The mean EAT volume was 128.3 ± 65.0 cm^3 in survivors and 154.6 ± 84.5 cm^3 in nonsurvivors ($p = 0.02$). The density of EAT was −79.4 ± 8.3 HU in survivors and −76.0 ± 8.4 HU in nonsurvivors ($p = 0.86$), and EAT density was associated with 30-day mortality (odds ratio [OR] = 1.07; 95% confidence interval [CI]: 1.03; 1.1, $p < 0.001$) but did not remain statistically significant in multivariable analysis. No association was identified between EAT volume and 30-day mortality (OR = 1.0; 95% CI: 1.0; 1.0, $p = 0.48$).
Conclusion: There might be an association between EAT density and mortality in patients with acute pulmonary embolism. Further studies are needed to elucidate the prognostic relevance of EAT parameters in patients with acute pulmonary embolism.

Keywords
Epicardial adipose tissue · Computed tomography · Pulmonary embolism

Acute pulmonary embolism (PE) is a possible life-threatening cardiovascular disease with 30-day mortality rates ranging from 0.5% to over 20% depending on clinical symptoms at presentation [1, 2]. Yet, there are also low-risk clinical courses without severe complications and good clinical outcome [3]. An immediate risk stratification of patients with acute PE at the time of presentation is of great importance in order to characterize and identify patients at risk and to possibly escalate the treatment regimen [3].

Computed tomography pulmonary angiography (CTPA) is an established diagnostic modality in clinical routine [4–6]. It is considered the diagnostic gold standard for the diagnosis of PE, with a reported sensitivity and specificity up to 100% [4–6]. Most commonly, CTPA is performed directly at the time of the hospital admission to detect the PE [4]. Therefore, risk stratification based on CTPA could be very im-

Hans-Jonas Meyer and Alexey Surov contributed equally to the manuscript.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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portant [5]. There are already established imaging signs for the severe course of PE, which can be obtained via the CT images. Of these signs, the right-to-left ventricular diameter ratio has the strongest predictive value [5]. Another promising parameter is the contrast media reflux into the inferior vena cava [5, 7, 8].

Epicardial adipose tissue (EAT) is a type of visceral fat surrounding the myocardium and visceral layer of the pericardium. In certain conditions, EAT can secrete pro- and anti-inflammatory factors (e.g., adiponectin, interleukin [IL]-6, tumor necrosis factor (TNF)-α, and leptin) in the paracrine or endocrine pathways [9–11]. There is ample evidence that EAT is involved in the local regulation of myocardial and coronary function by modulating lipid metabolism and energy homeostasis. Clinically, the volume and thickness of EAT have been measured by cardiac magnetic resonance imaging (MRI), CT [9–11], and echocardiography [9–11]. As such, several studies have shown that enlarged EAT is associated with the occurrence and development of coronary artery disease [11]. The prognostic value of EAT was also evaluated in other diseases including Coronavirus disease 2019 [12]. However, it is unknown whether this parameter also holds prognostic information for patients with acute PE.

Therefore, the purpose of the present study was to investigate whether EAT is of prognostic relevance in patients with acute PE.

Methods

Patients

The present retrospective study was approved by the institutional review board of the University of Magdeburg (Nr. 145/21, Ethics Committee, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany).

Abbreviations

CT	Computed tomography
CTPA	Computed tomography pulmonary angiography
EAT	Epicardial adipose tissue
PE	Pulmonary embolism

All patients with acute PE were retrospectively assessed within the time period 2015–2021. Inclusion criteria were:

- Sufficient CT images with clearly visible PE at the admission to hospital
- Available clinical data regarding clinical signs, serological parameters, and follow-up
- No thrombolysis before and/or during the CT acquisition

Exclusion criteria were:

- Severe image artifacts (i.e., due to implants or motion artifacts) as well as any form of treatment
- Missing clinical data/follow-up
- Thrombolysis before CT imaging
- Chronic PE

Overall, 513 patients (216 female, 42.1%) were included in the analysis. The mean age at the time of CT acquisition was 64.9 ± 15.6 years (median age: 66 years).

Clinical parameters

The following clinical parameters were retrieved at the timepoint of hospital admission:

- Relevant clinical comorbidities (active malignant disease, surgery performed within the last 4 weeks, chronic lung disease, chronic heart failure)
- Blood pressure (mm Hg), heart rate (*n*/minute), need for intubation, need for vasopressor, need for intensive care admission
- The Simplified Pulmonary Embolism Severity Index (sPESI) score was calculated
- Mortality, assessed in number of days after diagnosis of PE

Imaging technique

Computed tomography was performed at admission for every patient without any previous treatment. Diverse multislice CT scanners were used (Siemens Somatom Definition AS+, Siemens Healthcare, Erlangen, Germany, or Canon Aquilion Prime, Canon Medical Systems, Ottawara, Japan). In all cases, an intravenous administration of an iodinated contrast agent (60–150 mL Accupaque 300 mg/mL, GE Healthcare Buchler GmbH & Co. KG, Braunschweig, Germany; or Imeron 300, Bracco Imaging Deutschland GmbH, Konstanz, Germany) was given at a rate of 3.0–4.0 mL/s via a peripheral venous line. Automatic bolus tracking was performed in the pulmonary trunk with a trigger of 100 Hounsfield units (HU). Typical imaging parameters were 100–120 kVp, 25–200 mAs (tube current modulated 50–400 mA), slice thickness 1 mm, and a pitch factor of 1.4.

The right/left ventricular diameter was assessed for every patient in an axial slice.

Epicardial adipose tissue

A trained radiologist (AA), blinded to patient outcomes, measured the EAT volume with a dedicated workstation using Intellispace Portal (Version 11; Philips, Amsterdam, The Netherlands). The EAT volume was calculated considering density values in the range between −30 and −190 HU for adipose tissue and respecting as anatomical limits the pulmonary artery bifurcation, the left atrium, and the aortic root as the upper limit and the diaphragm and the left ventricle apex as the lower limit; mean density in HU was also calculated. This was previously described in the literature [13]. The following parameters were calculated: EAT volume, density, and volume/body height. **Figure 1** displays a representative case of our patient sample.

Statistical analysis

The statistical analysis and graphics creation were performed using SPSS (IBM SPSS Statistics for Windows, version 225.0, IBM Corp., Armonk, NY, USA). Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Group differences were calculated with the Mann–Whitney test and Fisher exact test, when suitable. Correlation analysis using Spearman's test was carried out to elucidate associations between the parameters. Uni- and multivariable logistic regression analyses were employed to investigate the associations with 30-day mortality. In all instances, values of $p < 0.05$ were taken to indicate statistical significance.

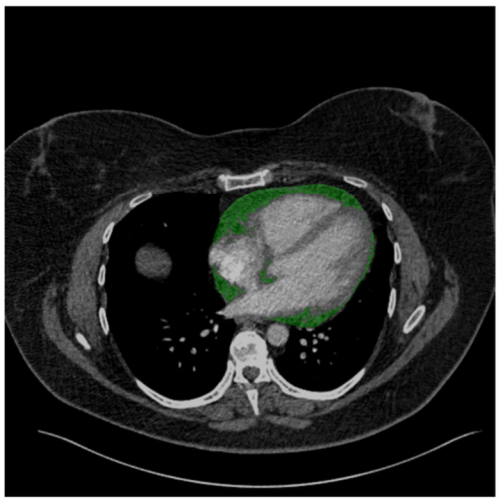

Fig. 1 ◀ Representative case from the patient sample with segmental acute pulmonary embolism. The epicardial adipose tissue (EAT) segmentation is visualized with a *green overlay*. The EAT volume is 415.2 cm^2 and the density is −82.7 HU

Results

Overall, 60 patients (11.7%) died within the 30-day observation period.

In survivors, the mean EAT volume was 128.3 ± 65.0 cm^3 and in nonsurvivors it was 154.6 ± 84.5 cm^3, $p = 0.02$. The density of EAT was −79.4 ± 8.3 HU in survivors and −76.0 ± 8.4 HU in nonsurvivors ($p = 0.89$; ◘ **Table 1**). Similar results were identified accordingly to hemodynamic stability of the patients (◘ **Table 2**).

Results showed that EAT volume correlated with age ($r = 0.17$, $p < 0.0001$) and systolic blood pressure ($r = 0.26$, $p < 0.0001$). However, EAT volume did not correlate with troponin level ($r = 0.07$, $p = 0.18$), lactate level ($r = -0.02$, $p = 0.73$), and right ventricular diameter ($r = 0.07$, $p = 0.08$).

Furthermore, EAT density correlated with systolic blood pressure ($r = -0.21$, $p < 0.0001$), right ventricular diameter ($r = 0.12$, $p = 0.0037$), and troponin level ($r = 0.17$, $p = 0.0021$).

There were no correlations between right–left ventricular diameter and EAT volume ($r = -0.06$, $p = 0.15$) and EAT density ($r = 0.04$, $p = 0.28$).

Finally, EAT density was associated with 30-day mortality in univariable logistic regression analysis (OR = 1.06; 95% CI [1.01; 1.08], $p < 0.001$; ◘ **Table 3**). Furthermore, EAT volume did not influence 30-day mortality (OR = 1.0; 95% CI [1.0; 1.0], $p = 0.48$). After adjustment with the sPESI score, EAT density was not associated with 30-day mortality in multivariable analysis (OR = 1.0; 95% CI [1.0; 1.0], $p = 0.38$).

Discussion

The present study sought to establish the prognostic relevance of EAT quantified with density and volume in patients with acute PE.

Correct and rapid risk stratification can be crucial for patients with acute PE. According to clinical guidelines, an important factor for a massive or critical course is hypotension with a systolic blood pressure below 90 mm Hg [3, 14, 15]. However, the absence of hemodynamic instability does not exclude beginning with a possibly progressing right ventricular dysfunction [15]. A standardized anamnestic and clinical evaluation comprises the Geneva and Wells score as a first assessment [15]. Regarding laboratory biomarkers, elevated troponin concentrations are associated with a worse prognosis [15]. Elevated B-type natriuretic peptide indicates right ventricular overload and is also associated with a worse prognosis in patients with acute PE [3, 15].

Echocardiography and CT can provide imaging information on right ventricular dysfunction but other reliable prognostic factors are still lacking to date [3, 15].

The prognostic and predictive implications of EAT have been extensively investigated in cardiovascular diseases, especially in coronary heart disease. The function of EAT in heart physiology includes its role in cardiac metabolism with mechanical protection of the coronary arteries, innervation, and potentially cryoprotection. However, recent evidence has revealed that EAT regulates multiple aspects of cardiac biology, myocardial redox state, and intracellular Ca^{2+} cycling [9–11]. It is noteworthy that electrophysiological and contractile properties of cardiomyocytes, and cardiac fibrosis, as well as atherogenesis are also regulated by EAT [9]. In a recent study of patients with diabetes, EAT volume was positively associated with age, BMI, pack-year history of smoking, and hypertriglyceridemia but negatively correlated with HDL cholesterol level [16].

Several studies elucidated a strong correlation between the severity of left ventricular diastolic dysfunction and the volume of EAT [17–19]. In acute PE, the prognostic relevance of EAT has not been systematically investigated until now.

The present analysis demonstrated some prognostic relevance of the density of EAT in patients with acute PE. The volume of EAT showed no association with 30-day mortality. Presumably, the inclusion of EAT into proposed risk scores such as the sPESI and the PEMS could increase the prognostic power of these scores [20].

The prognostic relevance of the density and not of the volume of EAT needs further consideration. The EAT volume was shown to be an important prognostic factor in patients with chronic coronary disease [9]. Yet, the quantification of the densities of adipose and muscle tissues is an emergent analysis, which might indicate earlier disease changes compared to the volume. For instance, there is recent evidence that muscle quality indicated by a decreased density of the muscle is an earlier finding of patients at risk compared to the muscle area [21–23]. Similar findings were reported for visceral adipose tissue in oncology patients [23]. Beyond that, in a recent study, the EAT density was also identified to be an important prog-

Table 1 Comparison between EAT parameters in survivors and nonsurvivors

Parameter	Survivors, M ± SD ($n = 452$)	Nonsurvivors, M ± SD ($n = 60$)	*p*
EAT volume (cm^3)	128.3 ± 65.0	154.6 ± 84.5	0.02
EAT density (HU)	−79.4 ± 8.3	−76.0 ± 8.4	0.0048
sPESI Score	1.2 ± 1.0	1.7 ± 1.1	0.0001
Heart rate (1/min)	95.5 ± 23.3	104.8 ± 34.6	0.13
Systolic blood pressure (mmHg)	134.0 ± 27.3	129.0 ± 38.6	0.10
D-dimer (mg/L)	5.2 ± 6.2	5.6 ± 5.7	0.81
Right/left ventricular diameter	1.1 ± 0.4	1.1 ± 0.5	0.48

EAT epicardial adipose tissue, *HU* Hounsfield unit, *M* mean, *SD* standard deviation, *sPESI* Simplified Pulmonary Embolism Severity Index

Table 2 Comparison between hemodynamic stable and instable

Parameter	Hemodynamic stable, M ± SD	Hemodynamic instable, M ± SD	*p*-value
EAT volume (cm^3)	130.59 ± 66.31	143.16 ± 88.59	0.03
EAT density (HU)	−79.0 ± 8.4	−78.8 ± 8.8	0.89

EAT epicardial adipose tissue, *HU* Hounsfield unit, *M* mean, *SD* standard deviation

Table 3 Univariable regression analysis to predict 30-day mortality

	Univariable			Multivariable		
Parameter	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
EAT volume (cm^3)	1.0	(0.89; 1.13)	0.87	–	–	–
EAT density (HU)	1.06	(1.01; 1.08)	< 0.001	1.0	(1.0; 1,0)	0.38
Gender	1.1	(0.70; 2.0)	0.50	–	–	–
Age	0.99	0.97; 1.009	0.34	–	–	–
Right/left ventricular diameter	1.00	1.0; 1.0	0.79	–	–	–
Heart rate	1.05	0.99; 1.01	0.34	–	–	–
Systolic blood pressure	0.99	0.98; 1.009	0.71	–	–	–
sPESI score	1.59	1.25; 2.05	0.001	1.59	1.25; 2.02	0.001

EAT epicardial adipose tissue, *HU* Hounsfield unit, *CI* confidence interval, *sPESI* Simplified Pulmonary Embolism Severity Index, *OR* Odds Ratio

nostic factor in patients with metabolic syndrome, showing better results when compared with EAT volume [24].

One important aspect of the present results is that EAT volume was statistically significantly different in the discrimination analysis, but did not remain significant in the logistic regression analysis. This could be interpreted as a possible signal that EAT volume could aid in the prediction of the prognosis but there might be a lack of statistical power in the present analysis.

It has to be acknowledged that manual EAT segmentation is a time-demanding procedure, which limits it translation into clinical routine. Yet, there are promising results that with the advent of artificial intelligence, new algorithms will be able to segment the EAT volume in a reliable manner [25]. This is a clear need for translation of EAT assessment of every patient with acute PET in clinical routine.

The present analysis is limited to a retrospective design with possible inherent bias. However, the EAT quantification was performed blinded to the clinical results in order to reduce possible bias. The present mortality rate of 10.4% is relatively high, which might be caused by selection bias. Moreover, it should be acknowledged that the present results might not be representative of patient samples with a lower case severity. Furthermore, the present study is based on a large cohort. To our best of knowledge, this is the first report on the associations between EAT and short-term mortality in acute PE.

Conclusion

In conclusion, there might be an association between epicardial adipose tissue (EAT) density and mortality in patients with acute pulmonary embolism. Further studies are needed to elucidate the prognostic relevance of EAT parameters in patients with acute pulmonary embolism.

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Declarations

Conflict of interest. A. Aghayev, M. Hinnerichs, A. Wienke, H.-J. Meyer and A. Surov declare that they have no competing interests.

All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This research was supported by the German Federal Ministry of Education and Research (BMBF) as part of the University Medicine Network (Project RACOON, 01KX2021).

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Zusammenfassung

Epikardiales Fettgewebe als prognostischer Marker bei akuter Lungenembolie

Hintergrund: Das epikardiale Fettgewebe ist mittlerweile bei koronarer Herzkrankheit als quantitativer bildgebender Biomarker als prognostischer Parameter etabliert. Ziel der vorliegenden Studie war es, diesen prognostischen Marker, der aus der Computertomographie-Pulmonalisangiographie (CPTA) abgeleitet wird, für die Vorhersage der Mortalität und Prognose bei Patienten mit akuter Lungenembolie zu untersuchen.
Methoden: Retrospektiv wurde die klinische Datenbank im Hinblick auf Patienten mit akuter Lungenembolie zwischen den Jahren 2015 und 2021 analysiert. Es wurden 513 Patienten (216 Frauen, 42,1%) in die aktuelle Auswertung einbezogen. Studienendpunkt war die 30-Tage-Mortalität. Das epikardiale Fettgewebe wurde anhand der diagnostischen CTPA in semiquantitativer Weise gemessen. Dabei wurde das Volumen und die Dichte des epikardiale Fettgewebes für jeden Patienten ermittelt.
Ergebnisse: Innerhalb der 30 Tage Beobachtungsdauer verstarben 60 Patienten (10,4%). Das mittlere Volumen des epikardialen Fettgewebes betrug $128,3 \pm 65,0\,cm^3$ bei den Überlebenden und $154,6 \pm 84,5\,cm^3$ bei den Nichtüberlebenden ($p = 0,02$). Bei den Überlebenden lag die Dichte des epikardialen Fettgewebes bei −79,4 ± 8,3 HU (Hounsfield-Einheiten) und den Nichtüberlebenden −76,0 ± 8,4 HU ($p = 0,86$).
Die Dichte des epikardialen Fettgewebes stand mit der 30-Tage-Mortalität in Zusammenhang (Odds Ratio [OR] = 1,07; 95%-Konfidenzintervall [95%-KI]: 1,03; 1,1; $p < 0,001$), blieb aber in der multivariablen Analyse nicht statistisch signifikant. Zwischen dem Volumen des epikardialen Fettgewebes und der 30-Tage-Mortalität fand sich kein Zusammenhang (OR = 1,0; 95%-KI: 1,0; 1,0; $p = 0,48$).
Schlussfolgerung: Möglicherweise besteht ein Zusammenhang zwischen der Dichte des epikardialen Fettgewebes und der Mortalität bei Patienten mit akuter Lungenembolie. Weitere Studien sind erforderlich, um die prognostische Bedeutung von Parametern des epikardialen Fettgewebes bei Patienten mit akuter Lungenembolie zu bestimmen.

Schlüsselwörter
Epikardiales Fettgewebe · Computertomographie · Lungenembolie

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Epicardial Adipose Tissue as a Prognostic Marker in COVID-19

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Abstract. *Background/Aim: Epicardial adipose tissue (EAT) has been established as a quantitative imaging biomarker associated with the prognosis of several diseases, especially cardiovascular diseases. The cardiac injury by coronavirus disease 2019 (COVID-19) might be linked to the EAT. This study aimed to use this prognostic marker derived from computed tomography (CT) images to predict 30-day mortality in patients with COVID-19. Patients and Methods: Consecutive patients with COVID-19 were retrospectively screened between 2020 and 2022. Overall, 237 patients (78 female, 32.9%) were included in the present study. The study end-point was the 30-day mortality. EAT was measured using the diagnostic CT in a semiquantitative manner. EAT volume and density were measured for each patient. Results: Overall, 70 patients (29.5%) died within the 30-day observation period and 143 patients (60.3%) were admitted to the intensive care unit (ICU). The mean EAT volume was 140.9±89.1 cm^3 in survivors and 132.9±77.7 cm^3 in non-survivors, p=0.66. The mean EAT density was –71.9±8.1 Hounsfield units (HU) in survivors, and –67.3±8.4 HU in non-survivors, p=0.0001. EAT density was associated with 30-day mortality (p<0.0001) and ICU admission (p<0.0001). EAT volume was not associated with mortality and/or ICU admission. Conclusion: EAT density was associated with 30-day mortality and ICU admission in patients with COVID-19.*

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Key Words: Epicardial adipose tissue, CT, COVID-19.

Epicardial adipose tissue (EAT) is a type of visceral fat located around the myocardium and pericardium. This type of fat is of endocrine importance, as EAT can produce pro- and anti-inflammatory factors including adiponectin, Interleukin-6, tumor-necrosis factor α and leptin (1-3). There is increasing scientific evidence that EAT regulates the function of the myocardium and coronary state by influencing the energy homeostasis as well as lipid metabolism.

The thickness of EAT as a diameter on one imaging slice as well as the volume of the whole EAT can be measured by cross-sectional imaging comprising cardiac magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography (1-3). Notably, various analyses have shown that enlarged EAT is associated with the incidence and prognosis of coronary artery disease (3).

The ongoing coronavirus disease 2019 (COVID-19) pandemic continues to affect the world and remains a threat to the health systems around the world. The clinical course of COVID-19 is highly variable with a mild course but also lethal cases. As such, a small group of the infected patients can suffer from a severe or critical course with admission to intensive care unit (ICU) or even with a fatal outcome (4-7). Noteworthy, the mortality rate during the first wave of the pandemic was high with over 10% of cases in most European countries (4, 5). There is no doubt that rapid and correct prediction of a fatal patient course of COVID-19 can help daily patient care (4, 5).

Early in the pandemic, clinical prognostic factors were identified, highlighting male sex and age with over 60 years with reported hazard ratios of 2.6 for age of 60 years and 1.4 for male sex, respectively (8, 9). CT plays a crucial role in diagnosis of COVID-19, especially in detecting pulmonary consolidations and the amount of involvement (10-12).

Early in the course of the pandemic, cardiovascular diseases were identified as a crucial risk factor in COVID-19 (9). Moreover, the direct cardiac injury of infected myocardial cells was mediated by the ACE2 receptors. This resulted in the release of immune-related factors, termed inflammatory storm, that could further lead to an imbalance of the oxygen supply (13). The association between EAT and the prognosis of COVID-19 might be caused by this cardiac

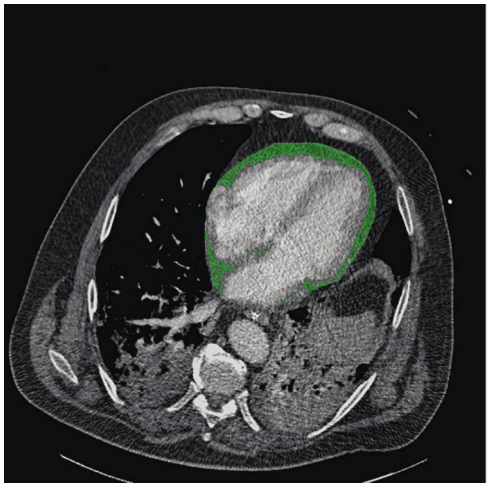

Figure 1. *A representative case of a patient sample with COVID-19. The EAT segmentation is visualized with a green overlay. The resulting EAT volume is 40.9 cm^3 and the density is –79.9 HU.*

involvement of the coronavirus. EAT assessment from CT images could provide novel biomarker. The prognostic value of EAT for COVID-19 was also evaluated in preliminary studies (14-17). Yet, due to the clinical differences of COVID-19 throughout the pandemic novel data is needed to evaluate the prognostic value of EAT.

The aim of the present analysis was to investigate, whether EAT is of prognostic relevance and shows associations with mortality and clinically relevant parameters in patients with COVID-19.

Patients and Methods

Patient acquisition. This present retrospective analysis was conducted 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. It received ethical approval from the local ethics committee following blinded review.

All consecutive patients diagnosed with COVID-19 were screened within the time period 2020 to 2022. Inclusion criteria were: CT imaging at the time point of the admission to the hospital; clinical data regarding the outcome; PCR-proven COVID-19 infection. Exclusion criteria were: severe image artifacts, which could hinder the measurement of EAT; missing clinical data/follow up.

Clinical data. The retrieved clinical data from the patients' records comprised: Age, sex, admission to ICU, duration of ventilation in hours, 30-day mortality.

CT imaging. All CT scans were obtained on a multidetector CT scanner (Siemens Somatom Definition AS+; Siemens Healthcare, Erlangen, Germany). During the first time of the pandemic, the scanner was used to scan every patient suspected or confirmed to be infected with COVID-19. Typical imaging parameters included a slice thickness 1 mm with 5 mm reconstructions, tube voltage 120 kV, automatic tube current modulation, pitch factor 1.2, and collimation 0.6 mm. In all cases contrast media was given.

Epicardial adipose tissue. A trained radiologist blinded to the clinical results, measured the EAT volume with the software Intellispace portal (Version 11; Philips, Amsterdam, the Netherlands). EAT volume was calculated using the density threshold between –30 and –190 Hounsfield units (HU) to semiautomatically segment fat tissue. Then, the anatomical limits were manually drawn to include the epicardial fat only. Of this segmented volume, the volume and the mean density in HU was calculated. This calculation was previously described in the literature (17). Figure 1 provides visualization of the EAT volume segmentation of a representative patient of the study cohort.

Statistical analysis. The statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows. version 225.0: IBM corporation, Armonk, NY, USA). The figures were created using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA). The retrieved data were first evaluated with descriptive statistics. Associations between EAT parameters and clinical features were assessed using Spearman's correlation coefficient. Discrimination analysis between groups were performed using Mann-Whitney test and Fisher exact test, when suitable. Uni- and multivariable logistic regression analysis were further used to investigate the associations between EAT parameters with 30-day mortality. In all instances, *p*-values <0.05 were taken to indicate statistical significance.

Results

Overall, 237 patients (78 female, 32.9%) were included into the analysis. The mean age at the time of CT-acquisition was 63.4±15.3 years, median age 65 years. In total, 70 patients (29.5%) died within the 30-day study observation period and 143 patients (60.3%) needed the admission to the ICU. The mean EAT volume in survivors and non-survivors was 140.9±89.1 cm^3 and 132.9±77.7 cm^3, respectively (p=0.66). Mean EAT density was –71.9±8.1 HU in survivors and –67.3±8.4 HU in non-survivors, (p=0.0001, Figure 2; Table I). A moderate inverse correlation was found between EAT volume and EAT density (r=–0.38, p<0.0001, Figure 3).

In patients with ICU admission, the mean EAT volume was 138.9±82.3 cm^3. It was 138.0±91.5 in patients who did not need ICU admission, (p=0.71; Table II). Furthermore, EAT density was associated with 30-day mortality according to univariable analysis (OR=1.08; 95%CI=1.04-1.1; p<0.0001) and to multivariable analysis (OR=1.07; 95%CI=1.03-1.1; p<0.0001). EAT volume showed no association with 30-day mortality (OR=1.0; 95%CI=1.0, 1.0; p=0.88) (Table III). Finally, EAT density was associated with ICU admission according to univariable analysis (OR=1.11;

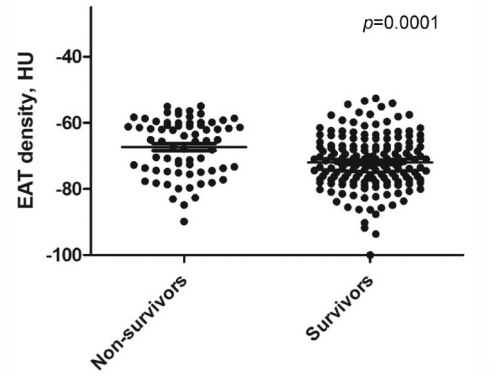

Figure 2. *Scatter plot of the EAT density in survivors and non-survivors. Mean EAT density was –71.9±8.1 HU in survivors and –67.3±8.4 HU in non-survivors, p= 0.0001.*

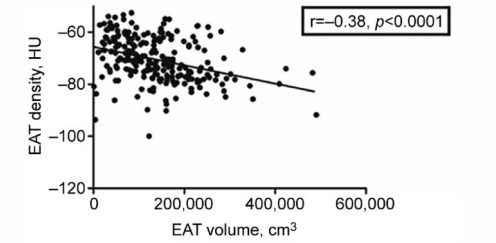

Figure 3. *Correlation analysis between EAT density and EAT volume. A moderate inverse correlation was identified (r=–0.38, p<0.0001).*

95%CI=1.06-1.13; p<0.0001) and multivariable analysis (OR=1.11; 95%CI=1.07-1.2; p<0.0001) (Table IV).

Discussion

The present analysis provides the prognostic relevance of EAT density and volume quantified from CT images in patients with COVID-19. As presented, there was an association between EAT density with 30-day mortality, whereas not with EAT volume. EAT density could serve as a novel useful biomarker quantified from CT images.

Correct and rapid risk-stratification can be crucial for patients with COVID-19 due to the different clinical courses (7, 8).

Very early during the pandemic, it was shown that cardiovascular disorders, especially coronary heart disease as co-morbidities are a risk factor for a severe COVID-19 course (18). The present analysis examined whether the known important factor of EAT as an important prognostic parameter in cardiovascular disease with the clinical outcome of COVID-19, which is known to cause direct cardiac injury including myocarditis.

An already established prognostic factor provided by CT imaging is the extension of pulmonary involvement of the consolidations. In a recent meta-analysis, there were promising results regarding the prognostic relevance of CT findings regarding coronary artery calcifications, mediastinal lymph adenopathy and pleural effusion in patients with COVID-19 (19). Noteworthy, the included patients were of the first wave of the pandemic with a different severity course and outcomes compared to recent days.

EAT was established as an important prognostic and predictive parameter in cardiovascular diseases, especially in coronary heart disease (1-3). The role of EAT comprises the cardiac metabolism with vasogenic effect on coronaries, innervation, and potentially the cryoprotection. However, recent data has revealed that EAT plays additional roles in cardiac biology, myocardial redox state and intracellular calcium cycling (1-3).

In a recent study on diabetes patients, EAT volume was positively associated with age, BMI, pack-year history of smoking, and triglyceridemia but negatively correlated with HDL cholesterol level (20). Marcucci *et al*. showed that the threshold value of 97 cm^3 had good diagnostic accuracy to predict a greater pulmonary manifestation course of COVID-19 (16). Contrary to these, in the present study the mean volume was higher than that reported by Marcucci *et al*., indicating a

Table I. *Comparison of the investigated EAT parameters between survivors and non-survivors.*

Parameter	Survivors, M±SD	Non-survivors, M±SD	*p*-Value
EAT volume (cm^3)	140.9±89.1	132.9±77.7	0.66
EAT density (HU)	–71.9±8.1	–67.3±8.4	0.0001

EAT: Epicardial adipose tissue; HU: Hounsfield unit; M: mean; SD: standard deviation.

Table II. *Comparison of EAT volume and density between patients with and without need for ICU admission.*

Parameter	ICU admission, M±SD	No ICU admission, M±SD	*p*-Value
EAT volume (cm^3)	138.9±82.3	138.0±91.5	0.71
EAT density (HU)	–68.1±7.8	–74.1±8.1	<0.0001

EAT: Epicardial adipose tissue; HU: Hounsfield unit; M: mean; SD: standard deviation; ICU: intensive care unit.

Table III. *Uni- and multivariable regression analysis to predict 30-day mortality.*

	Univariable			Multivariable		
Parameter	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
EAT volume (cm^3)	1.0	(1.0-1.0)	0.88	1.0	(1.0-1.0)	0.51
EAT density (HU)	1.08	(1.04-1.1)	<0.0001	1.07	(1.03-1.1)	<0.0001
Age	1.02	(1.003-1.05)	0.03	1.02	(0.99-1.03)	0.06
Sex	0.80	(0.41-1.50)	0.48	0.99	(0.55-1.80)	0.99

EAT: Epicardial adipose tissue; HU: Hounsfield unit: CI: confidence interval.

Table IV. *Uni- and multivariable regression analysis to predict ICU admission.*

	Univariable			Multivariable		
Parameter	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
EAT volume (cm^3)	1.0	(1.0-1.0)	0.93	1.0	(1.0-1.0)	0.35
EAT density (HU)	1.10	(1.06-1.13)	<0.0001	1.11	(1.07-1.2)	<0.0001
Age	0.99	(0.97-1.01)	0.49	0.99	(0.97-1.0)	0.29
Sex	1.3	(0.74-2.27)	0.35	1.3	(0.71-2.59)	0.38

EAT: Epicardial adipose tissue; HU: Hounsfield unit; CI: confidence interval.

different study population (16). The proposed threshold cannot be translated to the investigated patient sample in the present analysis. Similarly, Slipczuk *et al.* proposed a median value of 98 ml as the cut-off with prognostic relevance for mortality (21). However, in the study by Bihan *et al.*, the mean EAT volume was within the same scope as that in the present study (15). The importance of regional differences, co-morbidities, and overall body composition could account for these severe differences regarding EAT volume. In a recent study by Duyuler *et al.*, EAT thickness measured on an axial CT slice was an independent predictor for ICU admission (14). Noteworthy, EAT density was not as commonly investigated in the literature compared to the volume (17, 22). In the study by Eslami *et al.* EAT density did not show an association with mortality. In the other study, patients with the lower third of the EAT density had a 3.6-fold increased risk for the occurrence of pulmonary embolism (22).

The present study adds to the literature that the HU values of EAT seem to be better than the sole volume of EAT. Similar findings were reported for visceral fat areas where HU quantification seems to be more predictive than the area itself. However, there is definite need to harmonize the partially inflicting results regarding EAT volume and to adjust for time of the pandemic and other important co-factors.

The present study is not free of limitations. First, the present analysis is limited to a retrospective design with possible known inherent bias. However, the EAT quantification was performed blinded to the clinical results to reduce possible bias. Second, patients from different waves of the pandemic were pooled together in the present analysis. However, due to the small sample size there could be no further subanalyses to adjust for this fact.

In conclusion, EAT density is associated with 30-day mortality and need for ICU admission in patients with COVID-19.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

H.J.M. and A.A.: wrote the main manuscript text. H.J.M.: performed the statistical analysis. A.S. and J.B.: Study design and Supervision. M.H. and A.A.: Data extraction and analysis. All Authors reviewed and approved the final manuscript.

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Original article

Low subcutaneous adipose tissue and myosteatosis are prognostic factors after allogeneic hematopoietic stem cell transplantation

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SUMMARY

Objective: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative treatment option for several hematological neoplasms. This study aimed to assess the parameters of body composition as predictors of post-transplant overall survival (OS) and adverse events in patients with leukemia, myelodysplastic syndromes (MDS), and myeloproliferative neoplasms (MPN).
Methods: This was a retrospective study of 122 adult patients who underwent their first allo-HSCT. The CT-based semi-automated measurement of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), visceral-to-subcutaneous fat ratio (VSR), sarcopenia in terms of skeletal muscle index (SMI), and myosteatosis based on the skeletal muscle radiation attenuation (SM-RA) was performed. Cox regression analysis was used to assess the association of body composition parameters with OS.
Results: In the univariate analysis, low SAT and myosteatosis were associated with lower OS (hazard ratio [HR] 2.02, 95% confidence interval [CI] 1.16–3.51, $p = 0.01$) and (HR 2.50, 95% CI 1.48–4.25, $p =< 0.001$), respectively. This association remained significant after adjusting for relevant covariates, with HR 2.32, 95% CI 1.23–4.38, $p = 0.01$ and HR 2.86, 95% CI 1.51–5.43, $p =< 0.001$, respectively. On the contrary, VAT, VSR, sarcopenia, and sarcopenic obesity were not statistically significant in OS. Severe post-transplant adverse events were more common in the low SAT group (odds ratio [OR] 3.12, 95% CI 1.32–7.40, $p = 0.01$) and OR 3.17, 95% CI 1.31–7.70, $p =< 0.01$ in the age- and sex-adjusted analysis.
Conclusion: Low SAT and myosteatosis may contribute to an increased risk of post-transplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially life-saving procedure for several hematological malignancies [1]. Relevant indications for HSCT comprise acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPN), including chronic myeloid leukemia (CML), and myelodysplastic syndromes (MDS), depending on the stage of disease and risk factors [2–5]. Additionally, allo-HSCT remains a valuable therapeutic option for patients with multiply relapsed or poor-risk chronic lymphocytic leukemia (CLL) [6–8]. Allo-HSCT is associated with immediate and long-term complications, which can result in decreased quality of life and shortened life expectancy [1]. Studies on the influence of body composition parameters as predictors of overall survival (OS) and adverse events following allo-HSCT are scarce.

Obesity has been identified as a risk factor in hematological diseases [9,10]. According to a meta-analysis by Wallin et al., in

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2011, the risk of multiple myeloma (MM) was significantly elevated among obese patients (relative risk 1.21, 95% confidence interval [CI]: 1.08–1.35) [10]. Fuji et al., in 2014, reported that the risk of non-relapse mortality after allo-SCT was significantly higher in the overweight and obese group compared to the normal weight group (hazard ratio [HR] 1.19 and 1.43, respectively) [11].

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) can predict clinical outcomes in solid tumors [12,13]. In 2016, Takeoka et al. evaluated 56 patients with newly diagnosed MM. Their findings revealed a significant association between low SAT and poor 2-year OS (HR 4.05, 95%CI 1.24–13.19), p = 0.02) [14]. Moreover, a meta-analysis conducted by Aleixo et al., shed further light on the prognostic significance of adipose tissue in hematological malignancies. Patients categorized with low VAT demonstrated a twofold increase in mortality risk (HR 2.02, 95% CI 1.30–3.14, p = 0.004). Similarly, patients classified with low SAT exhibited an almost threefold greater mortality risk (HR 2.98, 95% CI 1.69–5.26, p = 0.0002) [15].

As per the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is defined as a progressive and widespread skeletal muscle disorder, this condition is confirmed by the presence of low muscle quantity or quality [16]. Radiological sarcopenia has been explored as a biomarker utilizing the opportunistic measurement of skeletal muscle from routine cross-sectional cancer imaging via CT and MRI scans, widely regarded as the gold standard for non-invasive assessment of muscle quantity [17]. In a recent meta-analysis, sarcopenia identified on CT examinations was found to be associated with OS rates in hematological diseases, including Diffuse Large B-cell Lymphoma (DLBCL) and leukemias HR 3.05 (95% CI 2.30–4.05, p < 0.00001) and HR 1.57 (95% CI 1.07–2.31, p < 0.02), respectively [18]. In 2019, Armenian et al. showed that sarcopenia assessed by measuring the skeletal muscle index (SMI) was an independent predictor of higher post-transplant mortality in patients with acute leukemia and MDS HR 1.58, 95% CI 1.16–2.16, $p = 0.004$) [19]. Besides the loss of skeletal muscle tissue (SMT), qualitative structural changes, such as the presence of inter- and intramyocellular fat deposition, a condition known as myosteatosis, can potentially impact clinical outcomes in hematological diseases [20].

Our study aimed at assessing the body composition parameters: VAT, SAT, sarcopenia, and myosteatosis based on the skeletal muscle radiation attenuation (SM-RA) as predictors of OS and adverse events in patients with leukemia, MDS, or MPN undergoing allo-HSCT.

2. Methods

2.1. Participants

This retrospective cohort study was approved by the Institutional Review Board (Nr. 145/21, Ethics Committee, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany). The requirement to obtain informed consent was waived.

Inclusion criteria were the following: (a) patients (≥18 years old) who underwent their first allo-HSCT for confirmed leukemia (acute or chronic, regardless of the phenotype), MDS, or MPN at the Department of Hematology and Oncology (University Hospital Magdeburg) between January 2015 and October 2021, (b) CT of the chest, abdomen, and pelvis before the transplant conducted within four weeks prior allo-HSCT. The exclusion criteria were as follows: (a) no available CT and (b) previous hematopoietic stem cell transplantation (HSCT). CT scans were performed to rule out occult infection before the initiation of conditioning therapy. Patients were identified in our internal clinical database (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Germany). Clinical information was extracted and comprised of gender, age, height, weight, body mass index (BMI), total serum protein (g/dL), total serum albumin (g/dL), and allo-HSCT donor source.

2.2. Overall survival and adverse events

OS was defined as the time from transplant to death or the date of the last contact in February 2023. Early post-transplant adverse events were retrieved from patients' medical records and graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) of the National Institutes of Health [21]. Early post-transplant adverse events were defined as those manifesting within the initial 30 days post-transplantation. After transplantation, patients were seen in our outpatient clinic every week and later every 4–8 weeks depending on their general condition and side–effect profile. Subsequently, follow-up intervals were extended.

2.3. CT technique and segmentation of body composition

CT scans were performed on a Canon Aquilion Prime (Canon Medical Systems, Otawara, Japan) or Siemens SOMATOM Definition AS+ (Siemens Healthcare, Erlangen, Germany) multidetector CT scanner. Patients were scanned in a supine position. The protocol was as follows: acquisition slices thickness of 1 mm with reconstructions of 5 mm, tube voltage of 120 kV, automated tube current modulation, pitch factor of 1.2., and collimation of 0.6 mm.

Our segmentation technique has been previously described [22,23]. In brief, we chose series with a 5 mm axial slice thickness and soft tissue kernel at the level of the third lumbar vertebra (L3). The cross-sectional areas of the SMT, SAT, VAT, and intermuscular adipose tissue (IMAT) were semiautomatically measured with the ImageJ software 1.48v (Wayne Rasband, National Institutes of Health, Maryland, USA). Furthermore, the mean SM-RA as an indicator of muscle density and myosteatosis was recorded in Hounsfield Units (HU). Skeletal muscle, was identified using threshold values of −29 and 150 HU. Fat areas were measured using HU threshold levels of −190 and −30 HU, as previously reported [23–26]. The software was operated by a researcher with four years of experience in the field of abdominal radiology, complex imaging analysis, and segmentation techniques, who was blinded to the patient's survival status (Fig. 1).

2.4. Definitions of body composition groups and myosteatosis

BMI was calculated by using the formula [weight (kg)/height squared (m^2)] [27]. Patients were categorized according to their BMI, as follows: (a) underweight (<18.5 kg/m^2), (b) normal weight (18.5–24.9 kg/m^2), (c) overweight (25.0–29.9 kg/m^2), and (d) obese (≥30 kg/m^2) [28]. The cut-off value for the classification of SAT was 100 (cm^2); for VAT 100 (cm^2); and for VSR ratio 1.1 [22,29]. Sarcopenia was defined depending on the SMI. The latter was calculated by dividing SMT (cm^2) by height squared (m^2) [27]. In accordance with the criteria established by Prado et al., radiological sarcopenia was defined using SMI cut-off values, for male patients, the SMI cut-off value was 52.4 cm^2/m^2, while for female patients, it was 38.5 cm^2/m^2 [30]. Sarcopenic obesity was defined as the occurrence of sarcopenia and increased BMI (>25 kg/m^2) [31]. Myosteatosis was defined as SM-RA < 41 HU for patients with a BMI ≤24.9 kg/m^2 and <33 HU for patients with a BMI ≥25.0 kg/m^2 [32,33].

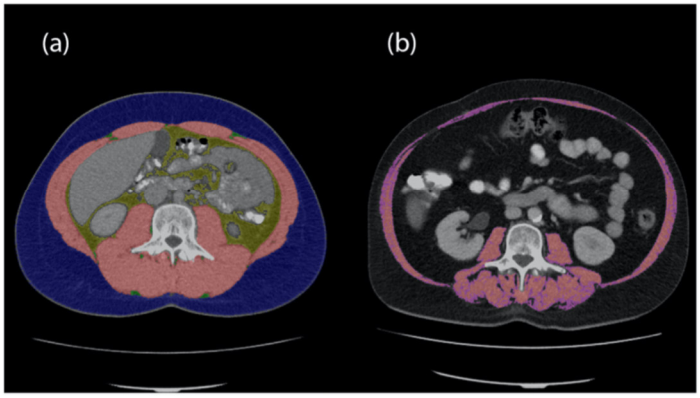

Fig. 1. CT-derived body composition at the third lumbar vertebral (L3) (a) blue, subcutaneous adipose tissue (SAT); pink, skeletal muscle tissue (SMT); green, intermuscular adipose tissue (IMAT); and yellow, visceral adipose tissue (VAT). (b) purple, skeletal muscle radiation attenuation (SM-RA). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.5. Statistical analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Descriptive statistics were presented as the median and interquartile range (IQR) for data with non-parametric distributions and as the mean and standard deviation (SD) for parametric distributions. The correlation between BMI and body composition parameters was calculated by Spearman's rank correlation coefficient. Univariate and Cox regression analysis was used to assess the association of body composition parameters (based on dichotomous traits) with OS. Cox regression models adjusted for relevant covariates (age, sex, graft-versus-host disease, organ failure, renal failure, post-transplant adverse events, and severe adverse events graded according to CTCAE [$\geq$4]) were also used to test this association. HRs are presented together with 95% CI. The Kaplan–Meier method was performed to estimate survival probabilities, which were compared between the groups of body composition using the log-rank test. Additionally, a binary logistic regression model (unadjusted and adjusted for age and sex) was performed to explore the association between the body composition groups as risk factors for specific early post-transplant adverse events and according to CTCAE (grade 3 or $\geq$ 4). Odds ratios (ORs) are presented together with 95% CI. A two-tailed p-value $\leq$0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) was used as analytic software.

3. Results

3.1. Participants

122 patients (68 males) were evaluated. The median age of the patients was 56.50 years (IQR: 44.00–64.00 years). The mean BMI was 26.16 ± 4.4 kg/m^2 51 (41.80%) and 23 (18.85%) patients were categorized as overweight and obese based on BMI, respectively. The most common diagnosis was AML in 59 patients (48.36%), followed by MDS in 20 patients (16.39%). The majority of the patients received their allo-HSCT from an unrelated donor [n = 101 (82.79%)], followed by a matched related donor in 17 cases (13.93%) (Table 1).

Table 1
Patient characteristics (n = 122).

Parameters	n, (%)
Female	54 (44.26)
Male	68 (55.73)
Age (years), median (IQR)	56.50 (44.00–64.00)
Body mass index (BMI) kg/m^2, mean ± SD	26.16 ± 4.4
Underweight (<18.5 kg/m^2)	3 (2.46)
Normal weight (18.5–24.9 kg/m^2)	45 (36.89)
Overweight (25.0–29.9 kg/m^2)	51 (41.80)
Obese (≥30 kg/m^2)	23 (18.85)
Total serum protein (g/dL)[a], mean ± SD	69.85 ± 6.8
Total serum albumin (g/dL)[b], mean ± SD	37.00 ± 0.87
Diagnosis	
Acute myeloid leukemia (AML)	59 (48.36)
Acute lymphoblastic leukemia (ALL)	8 (6.56)
Mixed-phenotype acute leukemia (MPAL)	4 (3.28)
Chronic lymphocytic leukemia (CLL)	12 (9.84)
Myeloproliferative neoplasms (MPN)	5 (4.10)
Myelodysplastic syndromes (MDS)	20 (16.39)
Others	14 (11.48)
Donor	
Matched-unrelated donor	101 (82.79)
Matched-related donor	17 (13.93)
HLA-haploidentical donor	4 (3.28)

Continuous variables are presented as mean (M) ± standard deviation (SD) or median and interquartile range (IQR).
[a] Information available for 120 patients.
[b] Information available for 82 patients.

3.2. Body composition parameters

Regarding the body composition parameters of our population, the mean SAT and VAT were 185.54 ± 102.2 cm^2 and VAT 140.97 ± 95.8 cm^2, respectively. The mean SM-RA density was 37.51 ± 9.2 HU. The median VSR was 0.66 [IQR 0.24–1.21]. 29 (23.77%) patients were classified in the group of low SAT, 75 (61.48%) in the group of high VAT, and 35 (28.7.%) in the group of high VSR. The median SMI was 43.55 cm^2/m^2 [IQR 37.9–52.35]. and Based on the sex-specific cutoffs, sarcopenia was identified in 69 patients (56.56 %), sarcopenic obesity in 30 (24.59%), and myosteatosis in 52 patients (43.62%) (Table 2).

Table 2
Body composition parameters of the patients ($n = 122$).

Body composition measurements (continuous variables)	n, (%)
SAT (cm^2), $m \pm SD$	185.54 ± 102.2
VAT (cm^2), $m \pm SD$	140.97 ± 95.8
VSR, *median, IQR*	0.66 [0.24–1.21]
SMT (cm^2), *median, IQR*	126.51 [106.92–157.73]
SMI (cm^2/m^2), *median, IQR*	43.66 [37.9–52.35]
IMAT (cm^2), *median, IQR*	7.83 [5.17–12.25]
SM-RA (HU), $m \pm SD$	37.51 ± 9.2
Body composition groups (based on dichotomous traits)	
Low SAT	29 (23.77)
High VAT	75 (61.48)
High VSR	35 (28.69)
Myosteatosis	52 (42.62)
Sarcopenia	69 (56.56)
Sarcopenic obesity	30 (24.59)

Continuous variables are presented as mean (m) ± standard deviation (SD) or median and interquartile range (IQR).
SAT, subcutaneous adipose tissue, VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio; SMT, skeletal muscle tissue; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; SM-RA, skeletal muscle radiation attenuation; HU, Hounsfield unit.

3.3. Association between body composition parameters and overall survival

Overall, 57 patients (46.7%) died during the evaluation period. The median OS time was 22.62 months (IQR: 7.07–58.01 months). In the univariate Cox regression analysis, low SAT and myosteatosis were associated with lower OS (HR 2.02, 95% CI 1.16–3.51, $p = 0.01$, adjusted: HR 2.32, 95% CI 1.23–4.38, $p = 0.01$) and (HR 2.50, 95% CI 1.48–4.25, p =<0.001, adjusted: HR 2.86, 95% CI 1.51–5.43, p=<0.001). On the contrary, high VAT, high VSR, sarcopenia, and sarcopenicobesity did not significantly influence OS (HR 0.93, 95% CI: 0.55–1.58, $p = 0.79$, adjusted: HR 0.79, 95% CI 0.47–1.78, $p = 0.91$) (HR 1.30, 95% CI 0.75–2.28, $p = 0.35$, adjusted: HR 1.88, 95% CI 0.89–3.98, $p = 0.10$) (HR 1.16, 95% CI 0.68–1.96, $p = 0.59$, adjusted: HR 1.19, 95% CI 0.68–2.08, p = 0.54), and (HR 0.82, 95% CI 0.43–1.55, $p = 0.54$, adjusted: HR 0.78, 95% CI 0.40–1.52, $p = 0.46$), respectively (Table 3). Similar results were observed in the Kaplan–Meier analysis (Fig. 2 and Suppl. Figure 1). There was a statistically significant difference between the groups of low SAT and high SAT and normal muscle density compared to myosteatosis regarding OS (log-rank test, $p = 0.01$ and p=<0.001, respectively).

3.4. Association between body composition parameters and post-transplant adverse events

We identified graft versus host disease (GVHD) in 52 out of 122 patients (42.62%), sepsis in 21 out of 122 (17.21 %), and organ failure in 38 out of 122 (31.15 %) patients, as detailed in Table 4. Subsequently, we evaluated the occurrence of these adverse events across different body composition groups). The results are presented in Suppl. Tables 2a, 2b, and 2c, outline the OR of body composition groups in relation to sepsis, GVHD, and organ failure, respectively. While the univariate analysis did not reveal significant associations between specific adverse events and body composition groups, myosteatosis emerged in the multivariate analysis as a significant risk factor for GVHD, with OR 3.49, 95% CI 1.46–8.32. Furthermore, we observed, that post-transplant adverse events grade 3 were reported in 70 patients (57.38.%), grade 4 in 43 (35.2%), and grade 5 in 7 (5.74%) (Table 5). Notably, regarding the analysis of body composition groups as risk factors for post-transplant complications according to CTCAE, we found that adverse events grade ≥4 were more likely to occur in patients with low SAT with OR of 3.12, 95% CI 1.32–7.40, $p = 0.01$ and OR 3.17, 95% CI 1.31–7.70, p = 0.01, after adjusting for sex and age.

3.5. Correlation analysis

The correlation analysis revealed significant associations between BMI and various body composition parameters (Suppl. Table 1). Specifically, BMI exhibited a strong positive correlation with SAT (r = 0.82, p < 0.01) and VAT (r = 0.68, p < 0.01). Additionally, BMI demonstrated a statistically significant positive correlation with SMT (r = <0.01, p < 0.01). However, a negative correlation was observed between BMI and SM-RA (r = −0.37, p < 0.01), indicating that higher BMI values were associated with lower skeletal muscle attenuation.

4. Discussion

Allo-HSCT has broad applications in treating various hematological malignancies [4–6]. Our study examined the association between parameters of body mass composition and OS after transplantation in leukemia, MDS, and MPN. Our findings suggested that low SAT and myosteatosis may contribute to an increased risk of post-transplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events.

According to a recent meta-analysis sarcopenia is related to lower OS in patients with hematological diseases that did not undergo allo-HSCT [18]. In acute leukemias and MDS, sarcopenia was associated with lower OS in the simple regression analysis (HR 3.05, 95% CI 2.30–4.05; $p = 0.00001$ and HR 1.57, 95% CI 1.07–2.31, p=<0.02). Nevertheless, multiple regression analyses showed no association between sarcopenia and a lower OS (HR 1.82, 95% CI 1.07–3.58). In this meta-analysis, two studies evaluating patients with leukemias/MDS were included [18]. In one of these studies, Nakamura et al. analyzed the three-year OS in 90 patients with AML who received chemotherapy and showed an association between

Table 3
Association between body composition parameters (as dichotomous traits) and overall survival ($n = 122$).

Parameters	Unadjusted			Adjusted*		
	HR	CI 95%	p-value	HR	95% CI	p-value
SAT (low vs. high)	2.02	[1.16–3.51]	0.01	2.32	[1.23–4.38]	0.01
VAT (high vs. low)	0.93	[0.55–1.58]	0.79	0.79	[0.47–1.78]	0.91
VSR (high vs. low)	1.30	[0.75–2.28]	0.35	1.88	[0.89–3.98]	0.10
SM-RA (myosteatosis vs normal muscle)	2.50	[1.48–4.25]	<0.001	2.86	[1.51–5.43]	<0.001
Sarcopenia (yes vs. no)	1.16	[0.68–1.96]	0.59	1.19	[0.68–2.08]	0.54
Sarcopenic obesity (yes vs. no)	0.82	[0.43–1.55]	0.54	0.78	[0.40–1.52]	0.46

Cox regression models were adjusted for age, sex, graft-versus-host disease, organ failure, renal failure, sepsis, and severe adverse events graded according to CTCAE (≥4). HR, hazard ratio; CI, confidence interval; SAT, subcutaneous adipose tissue, VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio, SM-RA, skeletal muscle radiation attenuation.

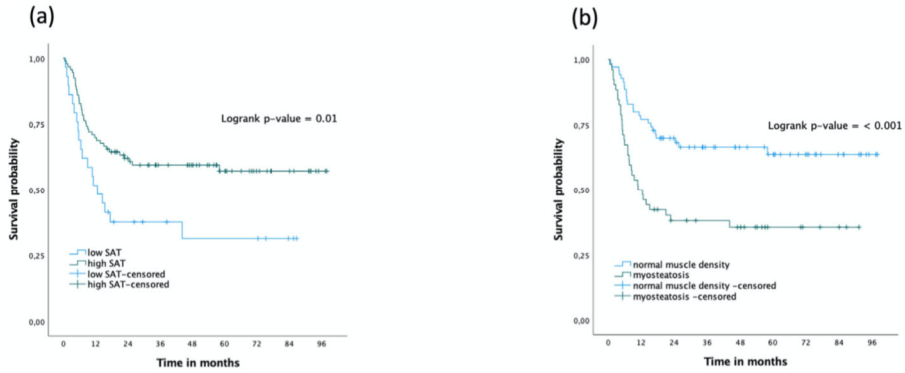

Fig. 2. Results of the Kaplan–Meier survival analysis for patients stratified according to (a) the subcutaneous adipose tissue (SAT) and (b) SM-RA, skeletal muscle radiation attenuation.

Table 4
Post-transplant adverse events (n = 122).

Adverse events after allo-HSCT	*n*, (%)
Fever	97 (79.51)
GvHD	52 (42.62)
Mucositis	42 (34.43)
Organ failure	38 (31.15)
Viral reactivation	37 (30.33)
Diarrhea	32 (26.23)
Renal failure	24 (19.67)
Sepsis	21 (17.21)
Thrush	19 (15.57)
Exanthema	17 (13.93)
Pneumonia	13 (10.66)
Urinary tract infection	13 (10.66)
Palmar-plantar-erythrodysesthesia	9 (7.38)

Allo-HSCT, Allogeneic Hematopoietic Stem Cell Transplantation, GvHD, Graft versus host disease.

sarcopenia and lower OS (HR 2.27, 95% CI 1.11–4.79, p=<0.005) [34]. In the other study, Armenian et al. conducted a retrospective observational analysis of sarcopenia as a prognostic factor in patients with AML, ALL, and MDS after transplantation [19]. They found that pre-transplant sarcopenia was an independent predictor of higher nonrelapse mortality during the first two years after transplantation (HR 1.58, 95% CI 1.16–2.16). In our study, sarcopenia and sarcopenicobesity did not significantly influence OS (HR 1.16, 95% CI 0.68–1.96, p = 0.59, adjusted: HR 1.19, 95% CI 0.68–2.08, p = 0.54), and (HR 0.82, 95% CI 0.43–1.55, p = 0.54, adjusted: HR 0.78, 95% CI 0.40–1.52, p = 0.46). The reason for this is not apparent ultimately, multi-centric studies are required to harmonize these discordant results regarding the role of pre-HSCT sarcopenia and OS.

Regarding the post-transplant complications, in our study, sarcopenia and sarcopenic obesity were not identified as risk factors for post-transplant adverse events grade ≥4 (OR = 0.96, 95% CI:0.46–1.99, p = 0.92, age and sex-adjusted: OR 0.95, 95% CI 0.42–2.15, p = 0.90) and (OR 0.53, 95% CI 0.22–1.29, p = 0.16, age and sex-adjusted: OR 0.55, 95% CI 0.23–1.34, p = 0.19), respectively. Suzuki et al. retrospectively assessed sarcopenia in 47 patients with ALL who underwent induction therapy. In their study, adverse events of grade 3 or greater were more likely to occur in sarcopenic patients than in non-sarcopenic (50.1% and 12.1%, p = 0.009) [35]. In their study, sarcopenia was measured by evaluating the psoas muscle area manually. Since the SMI is broadly considered a more complete and robust measurement of the skeletal muscle status and a strength of our study is the use of a semi-automated tool for

Table 5
Odds ratio of body composition groups and post-transplant adverse events (n = 122).

CTCAE grade 3 (n = 70)	Univariate analysis			Age and sex-adjusted		
	OR	CI	*p*-value	OR	CI	p-value
SAT (high vs. low SAT)	2.84	[1.20–6.71]	0.02	0.35	[0.15–0.85]	0.02
VAT (high vs. low VAT)	1.75	[0.84–3.67]	0.14	0.58	[0.25–1.35]	0.21
VSR (high vs. low VSR)	0.99	[0.45–2.18]	0.97	1.23	[0.48–3.17]	0.57
Myosteatosis vs normal muscle density	1.02	[0.49–2.11]	0.95	0.71	[0.25–2.06]	0.53
Sarcopenic vs. non-sarcopenic	1.06	[0.51–2.18]	0.88	1.04	[0.50–2.15]	0.92
Sarcopenic obesity vs non-sarcopenic obesity	2.05	[0.85–4.95]	0.11	0.35	[0.11–1.11]	0.07
CTCAE grade ≥ 4 (n = 50)	**OR**	**CI**	***p*-value**	**OR**	**CI**	**p-value**
SAT (low vs. high)	3.12	[1.32–7.40]	0.01	3.17	[1.31–7.70]	0.01
VAT (high vs. low VAT)	0.51	[0.24–1.07]	0.07	0.53	[0.23–1.23]	0.14
VSR (high vs. low VSR)	0.94	[0.42–2.10]	0.89	0.82	[0.31–2.12]	0.67
Myosteatosis vs normal muscle density	0.96	[0.46–1.99]	0.91	0.95	[0.42–2.15]	0.90
Sarcopenic vs. non-sarcopenic	0.96	[0.46–1.99]	0.92	1.02	[0.49–2.12]	0.96
Sarcopenic obesity vs non-sarcopenic obesity	0.53	[0.22–1.29]	0.16	0.55	[0.23–1.34]	0.19

OR, odds ratio; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events. SAT, subcutaneous adipose tissue; VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio.

the assessment of body composition parameters, we cannot confirm these previous findings [35].

Our results suggest that myosteatosis as a surrogate of muscle quality may be a predictor of OS in leukemia, MDS, and MPN following allo-HSCT. In 2019, Mueske et al. conducted a prospective study of the presence and degree of chemotherapy-associated altered body composition parameters in 12 adolescents and young adults treated for ALL [36]. In their study, tissue volumes for adipose muscle and bone along the entire length of both tibias were calculated. Additionally, muscle-associated fat was assessed by quantitative CT and utilized as a marker of myosteatosis. They showed a significant decrease in muscle tissue volume during the pre-maintenance ALL therapy ($p = 0.001$) and increased muscle-associated fat volume, primarily during the delayed intensification period ($p = 0.001$). According to a meta-analysis by Aleixo et al., cancer patients classified with myosteatosis had a lower OS compared to non-myosteatosis patients (HR 1.75 95% CI 1.60–1.92, p=<0.00001) [37]. In this meta-analysis, 40 studies of solid tumors were included, and the effect of myosteatosis in leukemia, MDS, or MPN was not evaluated. Our study suggests that the clinical significance of myosteatosis can be broadened as a risk factor to hematological malignancies.

Browne et al. reported that the percentage of overweight/obese children with ALL increased from 25.5% at diagnosis to approximately 50% during the off-therapy period. In our study, 51 (41.80%) and 23 (18.85%) were categorized as overweight and obese, respectively [38]. Notably, only 3 (2.46%) of the patients were classified as underweight. In agreement with Yu Yan et al., we consider that the evaluation of changes in fat content in cancer patients is clinically relevant [39]. In our cohort, a marked increase in severe adverse events with a corresponding decrease in OS was noted in patients with low SAT. One possible explanation for the heightened risk observed in patients categorized as having low SAT, leading to a higher occurrence of severe adverse effects (CTCAE $\geq$4, irrespective of type), is rooted in the role of tissue-derived mesenchymal cells. It has been reported that these cells can inhibit cell growth in hematologic malignancies and induce T-cell inhibition in patients undergoing allo-HSCT [15]. Our results align with previous studies by Takeoka et al., who evaluated 56 patients with MM and reported a low SAT index being linked to a poorer 2-year OS (HR 4.05, 95%CI 1.24–13.19), $p = 0.02$) [14], and with the findings of Ebadi et al., who indicated that low SAT is associated with increased cancer mortality (HR 1.26, 95% CI 1.26–1.43; p =<0.001) [14,40]. Ebadi et al. analyzed the parameters of body composition, including total adipose tissue index, subcutaneous adipose tissue (SATI) index, and visceral adipose tissue (VATI) in 1437 gastrointestinal and respiratory tract cancer patients and 273 metastatic renal cell carcinoma [40].

In our study, high VAT and high VSR did not significantly influence OS (HR 0.93, 95% CI 0.55–1.58, $p = 0.79$, adjusted: HR 0.79, 95% CI 0.47–1.78, $p = 0.91$) (HR 1.30, 95% CI 0.75–2.28, $p = 0.35$, adjusted: HR 1.88, 95% CI 0.89–3.98, $p = 0.10$). Our results are in line with Surov et al., who conducted an observational study of body composition parameters as prognostic factors for OS in MM after transplant [25]. In their study, regarding VAT, no significant association with OS was detected [HR 1.0 (CI 0.99–1.01), $p = 0.62$]. Multi-center studies with larger study populations should further explore the role of altered visceral adipose tissue in individual myeloid and lymphoid neoplasms.

Our study supports previous evidence by Alhomoud et al., in 2023, who asseverated that screening CT prior to transplantation is a beneficial tool to prevent potentially post-transplantation complications. In their descriptive analysis of 551 patients with leukemia, lymphoma, or MDS, abnormal clinical CT findings (such as consolidation and ground-glass opacification) were significantly associated with worse OS ($p = 0.032$) [41]. Our results suggest that the assessment of pretransplant CT scans has clinical significance beyond the evaluation of occult infection. The CT-based evaluation of body composition parameters, particularly SAT and SM-RA as an indicator of myosteatosis, is not only clinically significant but also feasible and reproducible in hematological malignancies, particularly with the help of semi-automated segmentation methods.

Our study has several limitations; firstly the study population encompassed a broad spectrum of hematological malignancies, potentially introducing heterogenicity into the analysis. The role of comorbidities or previous treatments, or adjuvant therapy as confounders was not explored. Additionally, the retrospective methodology and the monocentric setting limit the generalizability of our findings. One possible solution to address these limitations is to conduct multi-center studies with larger and more homogeneous study populations. Such studies would enable robust multivariate analyses exploring disease-modifying factors specific to individual neoplasms, which was not feasible in our study. Additionally, future research should aim to explore the role of altered body composition parameters in distinct myeloid and lymphoid neoplasms and evaluate the impact of multidisciplinary interventions of altered body composition parameters on clinical outcomes, including non-relapse mortality and progression-free survival and incorporating disease-modifying factors into our multivariate analysis to further refine our understanding of the complex interplay between body composition and disease outcomes.

In conclusion, low SAT and myosteatosis may contribute to an increased risk of post-tranplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events in patients with leukemia, MDS, or MPN after allo-HSCT. Integrating CT-based assessment of body composition parameters (particularly SAT and myosteatosis) into clinical protocols before allo-HSCT could aid in the identification of high-risk patients.

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Author contributions

A.S. and D.W. conceived and designed the study; Y.Z. A.A., H.K., and M.M. contributed to the collection of the clinical data, and M.H. performed the segmentation of the CT scans. F.B, Y.Z., and P.R. contributed to the manuscript writing. F.B., Y.Z., and P.R. contributed to the statistical analysis. D.M., D.W., and J.B. contributed to the critical revision of the manuscript. All authors approved the final manuscript for publication.

Declaration of competing interest

The authors have declared that no competing interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.03.032.

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9. Appendix

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9.2.Ehrenerklärung

Ich erkläre, dass ich die an der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel

Epikardiales, subkutanes und viszerales Fettgewebe als prognostische Marker bei diversen Erkrankungen

in der Universitätsklinik für Radiologie und Nuklearmedizin

mit Unterstützung durch Herrn Prof. Dr. med. Alexey Surov

ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Bei der Abfassung der Dissertation sind die Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

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9.3. Erklärung zur strafrechtlichen Verurteilung

Ich erkläre hiermit, nicht wegen einer Straftat verurteilt worden zu sein, die Wissenschaftsbezug hat.

Magdeburg, 01.03.2023

Unterschrift

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