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Prognostische Rolle der Magnetresonanz-Enterographie als multiparametrisches radiologisches Verfahren bei Patienten mit Morbus Crohn

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Publikation 1:

Thormann M, **Melekh B**, Bär C, Pech M, Omari J, Wienke A, Meyer HJ, Surov A. Apparent diffusion coefficient for assessing Crohn's disease activity: a meta-analysis. Eur Radiol [Internet]. European Radiology. 2022 Sep 28;33(3):1677–1686. Available from: https://link.springer.com/10.1007/s00330-022-09149-9 PMID: 36169687. (*nachfolgend Originalarbeit 1 genannt*)

Publikation 2:

Barajas Ordonez F, **Melekh B**, Rodríguez-Feria P, Melekh O, Thormann M, Damm R, Omari J, Pech M, Surov A. Body composition predictors of complicated Crohn's disease. Dig Dis. 2023 Jan 31. doi: 10.1159/000529426. Epub ahead of print. PMID: 36720207. (*nachfolgend Originalarbeit 2 genannt*)

Publikation 3:

Barajas Ordonez F, **Melekh B**, Rodríguez-Feria P, Damm R, Thormann M, March C, Omari J, Pech M, Surov A. Parameters of body composition and creeping fat are associated with activity of Crohn's disease. Magn Reson Imaging. 2023 Jan 10;98:1-6. doi: 10.1016/j.mri.2023.01.005. Epub ahead of print. PMID: 36634829. (*nachfolgend Originalarbeit 3 genannt*)

Publikation 4:

Melekh B, Barajas Ordonez F, Melekh O, Flintrop W, Pech M, Surov A. Diagnostic value of apparent diffusion coefficient of psoas muscles for evaluating complication in patients with Crohn's disease. Prz Gastroenterol. 2024;4(19):1-7.doi:10.5114/pg.2024.134519 (*nachfolgend Originalarbeit 4 genannt*)

Kurzreferat

Gemäß den fachlichen Empfehlungen der European Society of Gastrointestinal and Abdominal Radiology und der European Society of Pediatric Radiology spielt die MRT-Enterographie eine entscheidende Rolle bei der Beurteilung von gastrointestinalen Läsionen bei Patienten mit Morbus Crohn (MC). Aktuell hat sich das diagnostische Spektrum radiologischer Untersuchungen durch die Einführung teilautomatisierter Methoden der Bildanalyse und die Verwendung diffusionsgewichteter Sequenzen (DWI) sowie apparent diffusion coefficient (ADC) deutlich erweitert. Diese Verfahren ermöglichen die Bewertung von Veränderungen in den Zusammensetzungsparametern des Körpers und haben bedeutsame Ergebnisse im Kontext der Behandlung und Prognose von onkologischen Patienten gezeigt.

Der Zweck unserer Arbeit war: Analyse der Rolle von ADC bei der Beurteilung der Krankheitsaktivität bei MC-Patienten in Studien mit Magnetresonanz-Enterographie (MR-Enterographie) (*Originalarbeit 1*); Beurteilung der Körperzusammensetzungsparameter und des creeping fat (CrF) als Prädiktoren für die MC-Aktivität basierend auf dem Magnetic Resonance Index of Activity (MaRIA) in MC-Patienten mithilfe der MR-Enterographie (*Originalarbeit 2 und 3*); Beurteilung des Zusammenhangs zwischen ADC-Werten der Skelettmuskulatur und der Aktivität oder dem Verhalten von MC als Hochrisikomerkmalen (*Originalarbeit 4*).

Die 1. Originalarbeit zeigte, dass mäßige bis starke Assoziationen zwischen ADC und Crohn's Disease Activity Index (CDAI), MaRIA und endoscopic activity score (SES-CD) bestehen, und daher der ADC-Wert als wichtiges Instrument für die MC-Krankheitsaktivität verwendet werden kann. Die Rolle des ADC bei der Beurteilung fibrotischer Veränderungen in der Darmwand ist jedoch begrenzt. ADC-Werte können akute Entzündungsreaktionen widerspiegeln, aber keine systemische Entzündung. Die 2. Und 3. Originalarbeit fand den deutlichen Zusammenhang zwischen CrF und einem schweren MC-Verlauf sowie eine signifikante Verbindung zwischen CrF und einem hohen Verhältnis von viszeralem zu subkutanem Fettgewebe (VAT/SAT) mit dem Auftreten von Fisteln. Die 4. Originalarbeit zeigte, dass die ADC-Werte bei MC-Patienten, insbesondere solchen mit einer Striktur, signifikant niedriger waren. Diese Befunde legen nahe, dass der ADC zur Identifikation von Patienten mit ungünstigem Krankheitsverlauf genutzt werden kann, insbesondere zur Unterscheidung zwischen komplizierten und unkomplizierten MC-Verläufen.

Schlüsselwörter:

Magnetresonanzenterographie, Morbus Crohn, viszerales Fettgewebe, subkutanes Fettgewebe

Inhaltsverzeichnis

1. Abkürzungsverzeichnis

ACCENT 1	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen
ADC (engl.)	apparent diffusion coefficient
AIEC	adherent-invasive Escherichia Coli
BMI	Body-Mass-Index
CDAI (engl.)	Crohn's disease activity index
CED	chronisch entzündliche Darmerkrankungen
CT-Enterographie	Computertomographie-Enterographie
CrF (engl.)	creeping fat
CRP	C-reaktives Protein
CT	Computertomographie
CU	Colitis ulcerosa
DWI (engl.)	diffusion-weighted magnetic resonance imaging
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESPR	European Society of Pediatric Radiology ESPR
FCP	fäkales Calprotectin
HR (engl.)	hazard ratio
i.v.	intravenös
IMAT	intramuskuläres Fettgewebe
IMATI	intramuskulärer Fettgewebsindex
KI	Konfidenzintervall
IQR	Interquartilbereich
M	Mittelwert
MaRIA (engl.)	Magnetic Resonance Index of Activity
MC	Morbus Crohn
MR-Enterographie	Magnetresonanz-Enterographie
MRT	Magnetresonanztomographie
OR (engl.)	odds ratio
p.o.	per os
PACS (engl.)	Picture Archiving and Communication System
PMI	Psoas-Muskel-Index
r	Korrelationskoeffizient
RCE	relatives Kontrastmittelenhancement
ROI (engl.)	region of interest
SAT	subkutanes Fettgewebe
SATI	subkutaner Fettgewebsindex
SES-CD (engl.)	endoscopic activity score
SD	Standardabweichung
SMI	Skelett-Muskel-Index
SONIC	Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease
TAT	totales Fettgewebe
TATI	totaler Fettgewebsindex

VAT	viszerales Fettgewebe
VATI	viszeraler Fettgewebsindex
VAT/SAT	Verhältnis von viszeralem zu subkutanem Fettgewebe
WSI	Wandsignalintensität

2. Einführung

2.1 Inzidenz, Prävalenz und Risikofaktoren

Die weltweite Inzidenz und Prävalenz chronisch entzündlicher Darmerkrankungen (CED) nimmt stetig zu und betrifft derzeit etwa 0,2 % der europäischen Bevölkerung [1]. Ng et al. zeigten 2017 in ihrer systematischen Übersicht, dass 2030 schätzungsweise 1 % der Menschen, insbesondere in der westlichen Welt, durch CED betroffen sein wird [2]. Grundsätzlich gibt es zwei große Gruppen von Risikofaktoren: umweltbedingte und genetische Risikofaktoren. Beide neigen dazu, die Auswirkungen auf den menschlichen Körper zu verstärken und führen dementsprechend zu einer abnormalen Immunantwort [3].

Gastrointestinale Infektionen, nichtsteroidale Antirheumatika, Antibiotika, Rauchen und Appendektomie gehören zur umweltbedingten Risikofaktoren und ihr Einfluss wächst mit der Zeit stetig. Sie können eine Dysbiose verursachen und als Folge davon zu einer Verringerung der Diversität des Darmmikrobioms sowie einer Veränderung der Immunantwort führen [3]. Willing et al. haben in ihrer Studie darauf hingedeutet, dass die Menge von Bakterienpopulationen bei Individuen von allen MC-Phänotypen unterschiedlich ist. Zum Beispiel sind bestimmte Bakterien mit ilealem MC-Befall assoziiert [4]. Ormsby et al. wiesen 2019 darauf hin, dass die Prädominanz von adherent-invasiver Escherichia Coli (AIEC) im MC-Darm deutlich erhöht ist. Die erhöhten Produkte vom AIEC-Stoffwechsel wurden im Darm während des MC-Schubes identifiziert [5]. Die Entstehung einer Dysbiose wird auch durch den Einfluss von Viren und Pilzen verursacht. Sowohl MC als auch Colitis ulcerosa (CU) waren mit der Ausbreitung von Bakteriophagen der Familie Caudoviren verbunden [6].

Ein weiterer Faktor sind Antibiotika. Die Studie von Souradet et al. aus dem Jahr 2010 ergab, dass der Einsatz von Antibiotika in der frühen Kindheit das CED-Risiko erhöht, insbesondere bei MC [7]. Es wurde auch festgestellt, dass mehrere Behandlungen mit Antibiotika zu einem stärkeren Anstieg des Krankheitsrisikos beitragen [8].

Andere Faktoren, die das CED-Risiko erhöhen, sind Rauchen und Appendektomie. Mahid et al. zeigten 2006 in ihrer Metaanalyse, dass Rauchen ein Risiko, an MC zu erkranken, verdoppelt (odds ratio (OR) = 1,76, 95% Konfidenzintervall (KI) 1,40–2,22) [9]. Raucher benötigen eher eine Immunsuppression und einen chirurgischen Eingriff und haben eine größere Wahrscheinlichkeit eines Rezidivs nach einer Ileozökalresektion [10]. Ähnlich wie beim Rauchen hat sich auch die Appendektomie bei MC als negativer Faktor erwiesen. Der Zusammenhang zwischen Appendektomie und MC ist jedoch schwer zu interpretieren, da Patienten häufig wegen Bauchschmerzen operiert werden, bevor die MC-Diagnose gestellt

wird. Und dies kann wiederum zu falschen Ergebnissen hinsichtlich der Assoziation einer Appendektomie mit erhöhtem Risiko führen [3,10].

Neuere Studien zeigten eine wichtige Rolle genetischer Risikofaktoren bei der Pathogenese von CED [11]. Zwischen 2 % und 14 % der MC-Patienten und 8–14 % der CU-Patienten haben eine positive Familiengeschichte von CED [10]. Zwillingsstudien haben auch eine erbliche Schlüsselkomponente sowohl für MC als auch für CU nahegelegt [3,10].

Trotz der Identifizierung einer signifikanten Anzahl von CED-Risikofaktoren für das CED-Auftreten ist die Pathogenese dieser Erkrankung noch nicht vollständig geklärt [12,13]. Das hohe Wiederauftreten weist auf die Notwendigkeit hin, die Pathomorphologie dieser Krankheitsgruppe weiter zu erforschen, um Diagnose und Behandlung zu verbessern.

2.2 Klinik, Montreal-Klassifikation, und Komplikationen

Ein typischer CED-Vertreter ist MC als eine diskontinuierlich verlaufende, in Schüben auftretende Erkrankung, die jeden Teil des Magen-Darm-Trakts befällt und eine Reihe von Komplikationen auslösen kann [14]. Die Beteiligung des terminalen Illeums und des Dickdarms wird bei 50 % der Patienten beobachtet. 30 % der Patienten zeigen nur eine Beteiligung des Dünndarms und bei 20 % der Fälle ist MC nur im Dickdarm isoliert [3]. Der mediane Beginn der Erkrankung liegt im Alter von 30 Jahren und hat 2 Wellen, zuerst zwischen 20 und 30 Jahren und dann im Alter von etwa 50 Jahren [3,15]. Die MC-Symptome beginnen normalerweise bei Menschen in ihren Zwanzigerjahren. Mehr als 90 % der Patienten haben Symptome vor dem 40. Lebensjahr und weniger als 5 % werden nach dem 60. Lebensjahr diagnostiziert [16].

Je nach Art des Verlaufs werden nach der Montreal-Klassifikation folgende MC-Formen unterschieden: nicht strikturierend und nicht penetrierend, strikturierend, und penetrierend [17]. Eine nicht strikturierende und nicht penetrierende Form wird durch eine Entzündung des Darmtrakts ohne Zeichen einer Darmverengung oder Fistelbildung charakterisiert. Im weiteren Verlauf dieser Entzündung kann es zu fibrotischen Veränderungen mit Verengung des Darmlumens kommen, und das heißt eine strikturierende MC-Form. Diese fibrostenotischen Veränderungen sind vom pathomorphologischen Charakter irreversible Veränderungen, die nachfolgend einen chirurgischen Eingriff erfordern. Eine anhaltende transmurale Entzündung kann auch zur Entwicklung eines Fistelgangs führen, der für eine penetrierende MC-Form charakteristisch ist. Andere typische MC-Komplikation ist ein Abszess. Diese Komplikation bezieht sich auch auf die penetrierende Form. Diese Form ist oft durch ein akutes Abdomen gekennzeichnet und erfordert eine weitere chirurgische Behandlung.

Eine besondere Manifestation der penetrierenden MC-Form ist eine Schädigung der distalen Darmabschnitte mit dem Auftreten von Fisteln und Abszessen des Perianalbereichs. Perianaler MC ist eine schwächende Komplikation, die bei etwa 30 % der Personen mit Lumenerkrankung auftritt. Die Behandlung ist nach wie vor kompliziert und erfordert oft Operation in Kombination mit einer multimodalen Therapie [18].

2.3 Rezidive, Hospitalisation und Kosten

King et al. und Nguyen et al. zeigten 2019 bzw. 2020, dass trotz Fortschritten in therapeutischen Verfahren, insbesondere neuer biologischer Behandlungsmethoden, die Anzahl der Hospitalisation aufgrund typischer Komplikationen wie Fistelbildung und Abszessbildung hoch bleibt [19,20]. Ungefähr 80 % der Patienten müssen stationär behandelt werden, wobei 25 % innerhalb von 30–90 Tagen nach der Aufnahme wieder aufgenommen werden [19,20]. Die Progredienz der chirurgischen Behandlung wurde in einer Metaanalyse von Florkis et al. 2013 festgestellt. Etwa ein Drittel der MC-Patienten müssen innerhalb von 5 Jahren nach der Diagnosefeststellung operiert werden [21]. Auch das erhebliche Ausmaß wiederholter chirurgischer Rezidive ist derzeit ein akutes Problem. Die Inzidenz chirurgischer Rezidive betrug 11–32 % nach 5 Jahren, 20–44 % nach 10 Jahren und 46–55 % nach 20 Jahren [22]. Die Lösung des Problems ist die Identifizierung einer verbesserten Diagnostik, die den Entzündungsprozess besser beurteilen und die Risikofaktoren für ein Rezidiv identifizieren kann.

Trotz des Aufkommens neuer Medikamente steigen die Kosten für die Behandlung von Patienten, insbesondere in Westeuropa. Der Großteil aller direkten Gesundheitskosten entfällt auf medizinische und chirurgische Krankenhausaufenthalte und lag beispielsweise im Jahr 2020 bei etwa 3.500 € pro Patient und Jahr [1,23].

2.4 Übersicht der aktuellen Diagnostik

Die MC-Diagnose basiert sowohl auf klinischen Daten als auch auf laborchemischen, endoskopischen und radiologischen Untersuchungsmethoden. Die Symptome wie Bauchschmerzen, Durchfall, Übelkeit und Erbrechen sind meistens variabel, aber unspezifisch. Klinisch ist es oft schwierig, diese Symptome von Symptomen anderer Erkrankungen zu unterscheiden, insbesondere im Fall vom Reizdarmsyndrom, dessen Prävalenz 10- bis 50-mal häufiger als MC angegeben wird [24]. Das Krankheitsbild ist jedoch durch ein akutes oder unklares Abdomen gekennzeichnet und bleibt oft unspezifisch. Daher sollten zur Entscheidung

über eine Behandlungsstrategie subjektive klinische Ergebnisse mit objektiven Ergebnissen der Krankheitsaktivität durch biochemische Marker, Endoskopie oder radiologische Daten korreliert werden.

2.5 Endoskopische Verfahren

Die Endoskopie wird gegenwärtig als führende Methode zur CED-Diagnose betrachtet, insbesondere zur Unterscheidung zwischen CU und MC. Zudem spielt dieses Verfahren eine entscheidende Rolle bei der Überwachung der Krankheitsaktivität, der Bewertung der Behandlungseffektivität und der Erkennung von Komplikationen. Zu den endoskopischen Methoden zählen die Ileokoloskopie, die Ösophagogastroduodenoskopie, die Kapselendoskopie und die Ballon-Enteroskopie.

Modigliani et al. haben aufgezeigt, dass es eine Diskrepanz zwischen dem klinischen Bild und der Aktivität von MC gibt, die anhand von Endoskopien beurteilt wurde [25]. Sie haben festgestellt, dass das klinische Erscheinungsbild der Patienten nicht mit der Aktivität des pathologischen Prozesses korreliert. Es gibt auch keine signifikanten Zusammenhänge zwischen den Ergebnissen endoskopischer Verfahren und den Werten des C-reaktiven Proteins (CRP) oder fäkalen Calprotectins (FC). In den Studien ACCENT 1 (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) und SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) wurden fast 18 % der Patienten mit einem charakteristischen Krankheitsbild nicht erkannt [26,27]. Dies weist darauf hin, dass die Symptome der Patienten die Krankheitsaktivität nicht zuverlässig vorhersagen können und daher nicht als alleinige Grundlage für Behandlungsentscheidungen dienen sollten.

Es ist besonders bemerkenswert, dass die Beurteilung der Krankheitsaktivität und des Ausmaßes von Darmschäden durch den gleichzeitigen Einsatz von ergänzenden endoskopischen und radiologischen Methoden erheblich verbessert wird [25]. Endoskopische Verfahren ermöglichen lediglich die Beurteilung der Schleimhaut im gesamten Gastrointestinaltrakt, während die Computertomographie-Enterographie (CT-Enterographie) oder MR-Enterographie eine transmurale Beurteilung der Krankheit in Bereichen ermöglichen, die für herkömmliche endoskopische Methoden nicht zugänglich sind. Sie können auch penetrierende Komplikationen der Krankheit diagnostizieren [28,29]. Aktuelle klinische Studien zeigen, dass die Heilung der Schleimhaut bei der Endoskopie oder das radiologische Ansprechen auf medikamentöse Therapie mit besseren Langzeitergebnissen verbunden ist

2.6 Radiologische Verfahren

Gemäß den Empfehlungen von Experten der European Society of Gastrointestinal and Abdominal Radiology (ESGAR) und der European Society of Pediatric Radiology (ESPR) spielt die Schnittbildgebung eine entscheidende Rolle bei der Bewertung von MC-Läsionen [30]. Solche Techniken wie CT-Enterographie und MR-Enterographie sind wertvolle Methoden zur Beurteilung von Lumenentzündungen und extraintestinalen Komplikationen. Sie ermöglichen eine präzise Einschätzung des Schweregrads und sind nicht auf die Untersuchung des Dickdarms und des terminalen Teils des Ileums beschränkt [31–33].

Die CT-Enterographie zeigt eine hohe Sensitivität bei der Identifizierung von Darmläsionen bei MC. In einer Metaanalyse von 2015 zeigten Puylaert et al. die gleiche Genauigkeit der CT- Enterographie im Vergleich zur MR-Enterographie bei der Beurteilung der Aktivität und Lokalisation von MC (86 % und 84 % entsprechend) [32]. Die hohe Auflösung beider Methoden ist mit einer hohen Sensitivität für die Erkennung von entzündlichen Prozessen verbunden, die durch Fisteln, Abszesse und Strikturen kompliziert sein können. Trotz ihrer Vorteile weist die CT-Enterographie jedoch einige signifikante Einschränkungen auf. Zum einen handelt es sich um eine Röntgenuntersuchung, die Strahlenbelastung mit sich bringt, und sie ist daher nicht geeignet, die Effektivität der Behandlung in Bezug auf übermäßige Strahlenbelastung zu überwachen. Bislang wurde kein Verfahren zur Identifizierung der Aktivität des Entzündungsprozesses während der CT-Enterographie entwickelt. Aus diesen Gründen bleibt die CT-Enterographie hauptsächlich die bevorzugte Methode bei akuten Erkrankungen.

Die MR-Enterographie hat sich derzeit als die präferiete Methode bei der Untersuchung von CED-Patienten erwiesen. Diese bildgebende Technik ermöglicht gleichzeitig eine morphologische und qualitative Bewertung der Erkrankung. Dadurch kann die MR-Enterographie die Ausbreitung im Magen-Darm-Trakt beurteilen und den Schweregrad der Erkrankung sowie ihre Aktivität analysieren, um eine präzise Verbindung mit dem klinischen Status herzustellen. Die MR-Enterographie zeichnet sich durch ihre Multiplanarität, hohe Auflösung und die Möglichkeit einer Funktionsbeurteilung ohne ionisierende Strahlung aus, was ihr ein hohes diagnostisches Potenzial verleiht [31]. Sie ermöglicht die Beurteilung von Wandstärke, Lymphknotenschwellung, Geschwüren, Fisteln, Ödemen, Strikturen und extraintestinalen Komplikationen. Ein weiterer Vorteil der MRT gegenüber der Endoskopie besteht darin, dass sie auch die proximalen Darmabschnitte beurteilen kann, wo das Endoskop aufgrund von Stenosen nicht durchgehen kann.

Angesichts der zuvor genannten Vorteile der MR-Enterographie wurden mehrere Indizes entwickelt, um die Aktivität des Entzündungsprozesses zu bewerten. Ein weit verbreiteter Index in diesem Zusammenhang ist der Resonanzaktivitätsindex Magnetic Resonance Index of Activity (MaRIA). Dieser Index stützt sich auf verschiedene Faktoren wie Wanddicke, Signalintensität der Darmwand nach Kontrastmittelgabe, das Vorhandensein von Ödemen, Geschwüren, Pseudopolypen und vergrößerten Lymphknoten [34,35]. Buisson et al. haben in ihrer Studie die hohe Präzision dieses Indikators im Vergleich zu den Resultaten endoskopischer Untersuchungen demonstriert, insbesondere hinsichtlich der Einschätzung der Wiederherstellung der Schleimhaut. Die Bewertung der Schleimhautregeneration ist von Bedeutung für die Überwachung der Behandlung und hat Auswirkungen auf die zukünftige Prognose. [36].

Derzeit wird die Sicherheit der Verwendung von Kontrastmitteln bei MRT-Untersuchungen weiterhin diskutiert. Daher gewinnen Studien, die sich auf den Einsatz von Nicht-Kontrast-Methoden konzentrieren, insbesondere von diffusionsgewichteten Bildern für MC-Patienten, die regelmäßig überwacht werden müssen, an Bedeutung. Die diffusionsgewichtete Bildgebung (DWI) nutzt den Bildkontrast, der sich aus der unterschiedlichen Bewegung von Wassermolekülen zwischen Geweben ergibt, und gilt als ein wichtiges Instrument zur frühzeitigen Erkennung ischämischer Veränderungen in klinischen Zuständen. Einige Studien haben gezeigt, dass die Bilddaten, insbesondere wenn der apparent diffusion coefficient (ADC) verwendet wird, mit den gewonnenen endoskopischen Daten korrelieren, insbesondere wenn fibrotische Veränderungen in der Darmwand nachweisbar sind [37,38]. Dennoch hat der ADC bisher die Verwendung von Kontrastmitteln nicht ersetzt und macht daher weiterführende Forschung erforderlich.

2.7 Parameter der Körperzusammensetzung

MC-Patienten leiden häufig unter Gewichtsverlust, Anämie und Hypothermie, was oft mit Unterernährung und einem Malabsorptionssyndrom einhergeht. Dieses Syndrom tritt bei 85 % der MC-Patienten auf und führt zu Veränderungen in der subkutanen und viszeralen Fett- sowie Skelettmuskelmasse. Diese Parameter wurden als potenzielle Biomarker vorgeschlagen, die MC-Aktivität, die Wirksamkeit der Behandlung und die Notwendigkeit einer Darmresektion widerspiegeln können [39]. Eine Studie von Bamba et al. zeigte, dass das Auftreten von Sarkopenie, also dem Verlust von Skelettmuskelmasse, ein Prädiktor für eine Darmresektion sein kann [40]. Umgekehrt reduziert eine höhere Muskelmasse die postoperative Morbidität.

Die Rolle von viszeralem und subkutanem Fett ist noch weniger erforscht. Die Studien zum Fettgewebestatus bei MC-Patienten haben gezeigt, dass Adipositas mit vermehrten perianalen Komplikationen, höherer Krankheitsaktivität, häufigeren Krankenhausaufenthalten, kürzerer Zeit bis zur ersten Operation und der Notwendigkeit einer aggressiveren medizinischen Behandlung assoziiert ist [41,42]. Bei MC geht die Krankheitsentwicklung häufig mit dem Auftreten von lokal vermehrtem mesenterialem Fett um die befallene Darmschlinge, dem sogenannten creeping fat (CrF) einher, was ein charakteristisches Merkmal für den schweren Verlauf der Krankheit ist. Dieses Fett ist reich an entzündungsfördernden und profibrotischen Zytokinen. Eine Vielzahl von angeborenen und adaptiven Immunzellen, die in diesem Fett vorhanden sind, tragen zur Entstehung von Fibrose bei. Somit stellt CrF ein potenzielles therapeutisches Ziel für die MC-Behandlung dar und könnte ein vielversprechender Biomarker für die Vorhersage des Ansprechens auf medikamentöse Therapien sein [43]. Eine weiterführende Studie zu Veränderungen in viszeralen, subkutanen Fetten und CrF würde dazu beitragen, unser Verständnis der Pathogenese von MC zu vertiefen und dementsprechend sowohl diagnostische Methoden als auch Behandlungsansätze zu verbessern.

2.8 Zielsetzung der Arbeit

Die Anwendung teilautomatisierter Bildanalyse in der Radiologie und die Integration zusätzlicher Sequenzen erweitern heutzutage deutlich das diagnostische Potenzial der MRT-Untersuchungen. Wir sind der Auffassung, dass durch den Einsatz geeigneter Methoden in der MR-Enterographie nicht nur Veränderungen im Magen-Darm-Trakt, sondern auch in den Parametern der Körperzusammensetzung beurteilt werden können, was zu einer erheblichen Verbesserung der Diagnostik und Behandlung führen könnte.

Um die gestellte Aufgabe zu bewältigen, wurden die folgenden Fragestellungen weiterverfolgt:

1. Analyse der Rolle von ADC bei der Beurteilung der Krankheitsaktivität bei MC-Patienten in Studien mit MR-Enterographie (*Originalarbeit 1*).

2. Beurteilung der Körperzusammensetzungsparameter und des CrF als Prädiktoren für die CD-Aktivität basierend auf dem MaRIA-Score in MC-Patienten mithilfe der MR-Enterographie (*Originalarbeit 2 und 3*).

3. Beurteilung des Zusammenhangs zwischen ADC-Werten der Skelettmuskulatur und der Aktivität oder dem Verhalten von MC als Hochrisikomerkmalen (*Originalarbeit 4).*

3. Material und Methoden

3.1 Patientenkollektiv

Die retrospektive monozentrische Studie wurde in der Universitätsklinik Magdeburg durchgeführt und schloss alle Patienten ein, bei denen im Zeitraum vom 01.06.2010 bis 01.04.2020 MRE-Scans angefertigt wurden. Das Ziel der MRE-Scans war die Beurteilung des Krankheitsverlaufes, des Auftritts der Komplikationen und des Ansprechen auf die Therapie. Die klinischen Daten wie Geschlecht, Gewicht, Größe, Alter, Rauchen, Krankheitsdauer, CRP, Komplikationen (Striktur, Fistel, Abszess) sowie Medikamente und frühere Bauchoperationen wurden aus unserer internen Datenbank (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Deutschland) extrahiert. Diese Studie wurde gemäß den Grundsätzen der Deklaration von Helsinki durchgeführt und vom Institutional Review Board (Nr. 145/21) der Otto-von-Guericke-Universität Magdeburg, Deutschland, genehmigt.

3.2 Einschluss- und Ausschlusskrieterien

Bei der Erforschung der Darmveränderungen und Parameter der Körperzusammensetzung (die 2. und 3. Originalarbeit) wurden die folgenden Einschlusskriterien festgelegt: (1) die erste chronologisch verfügbare MRE; (2) anthropometrische Daten in den klinischen Aufzeichnungen. Die Ausschlusskriterien waren: (1) MRT des Beckens; (2) starke MRT-Artefakte. Die endgültige Population bestand aus 114 CD-Patienten mit insgesamt 114-MRE.

Bei der Erforschung von Veränderungen beider Psoasmuskeln (die 4. Arbeit) wurden die Kriterien für die Patientenauswahl etwas geändert. Unsere Einschlusskriterien waren: (a) endoskopisch und/oder histologisch bestätigte CD; (b) vollständige demografische und klinische Daten; (c) die erste chronologisch verfügbare MRE; (d) durchgeführte DWI ohne Qualitätsminderung. Die Ausschlusskriterien waren wie folgt: (a) unvollständige klinische Daten; (b) starke MRE-Artefakte; (c) MRT der Beckenregion. Daher wurden letztendlich 88 Patienten in unsere Studie aufgenommen.

3.3 MRE-Untersuchungstechnik

Jede MRE wurde auf einem 1,5-Tesla-MR-Scanner (Intera, Philips Healthcare, Best, Niederlande) in Rückenlage unter Verwendung eines Ganzkörper-Oberflächenspulensystems durchgeführt. Das Protokoll umfasste eine Vorbereitung mit Fasten über Nacht vor der Untersuchung. Die Darmausdehnung wurde durch orale Verabreichung von 1200 ml 2,5 % Sorbitol in kleinen Aliquots über 4 Stunden vor der Untersuchung erreicht. Die Hemmung der Darmperistaltik erfolgte durch eine intravenöse Injektion von 20 mg/ml N-Butylscopolamin

(Buscopan, Boehringer Ingelheim, Deutschland). Als Kontrastmittel wurde bei allen MRE Gadolinium (Gadovist, Bayer Vital, Leverkusen, Deutschland) in einer Dosis von 0,1 ml/kg Körpergewicht verwendet.

3.4. Magnetischer Resonanzaktivitätsindex (MaRIA)

Die CD-Aktivität haben wir mithilfe des magnetischen Resonanzaktivitätsindexes (Magnetic Resonance Index of Activity - MaRIA) ausgewertet, der im Segment mit den stärksten Veränderungen gemäß der Formel [1,5 x Wandstärke (mm) + 0,02 x relative Kontrastverstärkung (RCE)] geschätzt wurde. RCE wurde wie folgt berechnet: RCE = [Wandsignalintensität (WSI) nach Gadolinium – WSI Pregadolinium / (WSI Pregadolinium)] x 100 x [Standardabweichung (SD) Rauschen Pregadolinium/SD Rauschen Postgadolinium]. Das SD-Rauschen vor und nach der Gadoliniumverabreichung wurde als Durchschnitt von drei SD der außerhalb des Körpers gemessenen Signalintensität ermittelt.

3.5 Beurteilung von Creeping Fat

Das kriechende Fett wurde qualitativ als erhöhtes Bauchfett rund um den betroffenen Darmabschnitt in der axialen T1-Sequenz beurteilt.

3.6 Messung der ADC-Werte bieder Psoas-Muskeln

Die Bestimmung des ADC-Wertes beider Psoas-Muskeln erfolgte auf Höhe des dritten Lendenwirbels. Die Analyse umfasste die Messung des kumulativen mittleren ADC-Werts beider Psoas-Muskeln. Der ADC-Wert wurde gemessen, indem in ADC-Karten polygonale Regionen von Interesse (ROI) entlang der Konturen der Psoas-Muskeln gezeichnet wurden, wobei Fettbereiche und Gefäße vermieden wurden.

3.7 Messung der Parameter der Körperzusammensetzung

Die Beurteilung von Fett- und Muskelgewebe wurde mit dem speziellen halbautomatischen Tool AsanJ-Morphometry durchgeführt [44]. Die Messungen auf der Ebene des dritten Lendenwirbels umfassten die Einschätzung des viszeralen Fettgewebes (VAT), des subkutanen Fettgewebes (SAT), des gesamten Fettgewebes (TAT), des Skelettmuskelgewebes und des intramuskulären Fettgewebes (IMAT) in Quadratzentimetern basierend auf der Pixelanzahl. Darüber hinaus wurde das Verhältnis von viszeralem zu subkutanem Fett (VAT/SAT) berechnet. VATI und SATI wurden berechnet, indem VAT und SAT durch das Quadrat der

Körpergröße dividiert wurden. Die geschlechtsspezifischen Grenzwerte für VATI (niedriger vs. hoher VATI) lagen bei 44,0 cm^2/m^2 für Männer und 35,0 cm^2/m^2 für Frauen [45]. Die geschlechtsspezifischen Grenzwerte für SATI (niedriger vs. hoher SATI) lagen bei 40,0 cm^2/m^2 für Männer und 30,0 cm^2/m^2 für Frauen [45]. Die geschlechtsspezifischen Grenzwerte für VAT/SAT (niedrige vs. hohe VAT/SAT) betrugen 1,325 für Männer und 0,710 für Frauen [46]. Sarkopenie wurde anhand des SMI gemessen. Der SMI wurde berechnet, indem das Skelettmuskelgewebe (cm^2) durch die Körpergröße im Quadrat (m^2) geteilt wurde [46]. Die SMI-Grenzwerte lagen bei 43,0 cm^2/m^2 bei einem BMI von 25 kg/m^2 bzw. 53 cm^2/m^2 bei einem BMI von 25 kg/m^2 und bei Frauen bei 41 cm^2/m^2 [46,47]. Zusätzlich wurde der Psoas-Muskel-Index (PMI) berechnet, indem die Psoas-Muskelflächen auf beiden Seiten durch das Quadrat der Körpergröße des Patienten (cm^2/m^2) geteilt wurden.

3.8 Statistische Analyse

Alle Analysen wurden mit einem Statistiksoftwarepaket (SPSS Statistics für Windows, Version 27.0, IBM Corp., Armonk, NY, USA) durchgeführt. Kontinuierliche Variablen wurden als Mittelwert (M) und Standardabweichung (SD) oder Median und Interquartilbereich (IQR) ausgedrückt. Kategoriale Variablen wurden in Prozentsätzen dargestellt. Zur Beurteilung der Normalität der kontinuierlichen Variablen wurde der Kolmogorov-Smirnov-Test verwendet. Kontinuierliche Variablen wurden zwischen Gruppen mithilfe des Student-t-Tests oder des Mann-Whitney-U-Tests verglichen. Kategoriale Variablen wurden mit dem $\chi 2$-Test oder dem exakten Fisher-Test verglichen. Für die univariate und multivariate Analyse (angepasst an Alter, Geschlecht und BMI) wurden alle Patienten anhand ihrer VATI-, SATI- und VSR-Werte in Körperzusammensetzungsgruppen dichotomisiert. Der Intraclass-Korrelationskoeffizient (KI) wurde für jedes Paar von ADC-, PMI- und MaRIA-Werten berechnet, um die Intra- und Interobserver-Übereinstimmung zu bestimmen. Für CrF als kategoriale Variable wurde außerdem der Cohen-Kappa-Test verwendet, um die Übereinstimmung innerhalb und zwischen Beobachtern zu bewerten. Ein p-Wert von 0,05 wurde als statistisch signifikant angesehen.

4. **Ergebnisse eigener Arbeit**

Originalarbeit 1

Apparent diffusion coefficient for assessing Crohn's disease activity: a meta-analysis.

Thormann M, Melekh B, Bär C, Pech M, Omari J, Wienke A, Meyer HJ, Surov A.

Die MRT-Enterographie als nicht-invasive Methode zur Untersuchung des Gastrointestinaltrakts spielt eine entscheidende Rolle bei der MC-Diagnose. Sie ermöglicht die Bewertung der Entzündungsaktivität und möglicher Komplikationen in allen Darmabschnitten [48–52]. Klassische MRT-Enterographieprotokolle benutzen Gadoliniumsequenzen, deren Verwendung in letzter Zeit aufgrund der Anreicherung im menschlichen Körper kontrovers diskutiert wird [53–55]. Moderne MRT-Protokolle integrieren gemäß den Empfehlungen der Europäischen Gesellschaft für gastrointestinale und abdominale Radiologie DWI und ADC, die auf der Bewertung der chaotischen Bewegung von Wassermolekülen in biologischen Geweben basieren und das diagnostische Spektrum dieser Untersuchung erweitern [50,56]. Das Ziel dieser Arbeit bestand darin, die Funktion von ADC in der Bewertung der Krankheitsaktivität bei MC-Personen zu analysieren.

Unsere Metaanalyse umfasste 21 Studien mit insgesamt 1053 Patienten, wobei 496 (47 %) weiblich und 577 (53 %) männlich waren. Von den Studien waren 11 (52 %) prospektiv und 10 (48 %) retrospektiv angelegt. Die Größe der untersuchten Patientengruppen schwankte zwischen 20 und 229, wobei das durchschnittliche Alter bei 26,5 Jahren lag. Ergebnisse zu pädiatrischen Patienten wurden in drei Studien berichtet [57–59]. In der Gesamtstichprobe betrug der gepoolte Korrelationskoeffizient (r) zwischen ADC und CDAI war 0,8 (95 % Konfidenzintervall (KI) = [-0,94; -0,65]), $p < 0,000001$, bei einer Heterogenität von $\tau 2 = 0,01$ ($p = 0,06$) und einem I^2 von 71 %, zwischen ADC und MaRIA -0,66 (95 % KI = [-0,79; -0,53]), $p < 0,000001$, bei einer Heterogenität von $\tau 2 = 0,02$ ($p < 0,0001$) und einem I^2 von 83 %. Es wurde eine starke Assoziation zwischen ADC und SES-CD mit einer gepoolten Korrelation von -0,66 (95% KI = [-0,87; -0,46]), $p < 0,000001$, bei einer Heterogenität von $\tau 2 = 0,04$ ($p < 0,0001$) und einem I^2 von 88 % beobachtet. Die gepoolte Empfindlichkeit zur Unterscheidung zwischen betroffenen und nicht betroffenen Darmsegmenten betrug 0,89 mit einer Fläche unter der Kurve von 0,89.

Originalarbeit 2

Parameters of body composition and creeping fat are associated with activity of Crohn's disease.

Barajas Ordonez F, Melekh B, Rodríguez-Feria P, Damm R, Thormann M, March C, Omari J, Pech M, Surov A.

Neueste Studien haben gezeigt, dass veränderte Körperzusammensetzungsparameter die Lebensqualität, postoperativen Komplikationen, Krankheitsaktivität und Verhalten von MC-Patienten beeinflussen können [60,61]. Bei den Patienten mit Strikturen und Fisteln wurde ein erhöhtes VAT/TAT-Verhältnis festgestellt [62]. Die VAT-Zunahme wird als eigenständiger Risikofaktor für das MC-Rezidiv nach einer Operation betrachtet [63]. Zusätzlich geht ein komplizierter MC-Verlauf mit dem Auftreten von CrF einher [64]. Daher wurde in dieser Studie das Ziel verfolgt, die Beziehung zwischen den Körperzusammensetzungsparametern, CrF und der MC-Aktivität anhand des MaRIA-Score zu analysieren.

114 CD-Patienten, die sich zwischen Juni 2010 und April 2020 einer Magnetresonanz-Enterographie (MRE) unterzogen, wurden retrospektiv untersucht. Anhand des MaRIA-Score wurden die Patienten in zwei Gruppen eingeteilt: leichte bis mittelschwere Erkrankung (MaRIA <11, n = 50) und schwere Erkrankung (MaRIA ≥11, n = 64). Die Gruppe mit schwerer Erkrankung wies höhere CRP-Serumspiegel auf als die Gruppe mit leichter bis mittelschwerer Erkrankung ($p \leq 0{,}001$). In der Gruppe mit leichter bis mittelschwerer Erkrankung hatte ein höherer Anteil der Patienten einen BMI ≥ 25 kg/m2 (32,0 %), verglichen mit der Gruppe mit schwerer Erkrankung (16,5 %) ($p = 0{,}04$). SATI war in der Gruppe mit leichter bis mittelschwerer Erkrankung signifikant höher ($p = 0{,}04$). Das VAT/SAT-Verhältnis war in der Gruppe mit schwerer Erkrankung tendenziell höher ($p = 0{,}09$). Es gab keinen signifikanten Unterschied zwischen beiden Gruppen hinsichtlich des Gesamtfettgewebeindex (TATI) ($p = 0{,}10$), des VATI ($p = 0{,}51$), des intramuskulären Fettgewebeindex (IMATI) ($p = 0{,}38$) und der SMI ($p = 0{,}83$) und Sarkopenie ($p = 0{,}75$). In der multivariaten Analyse war CrF signifikant mit einer schweren Erkrankung assoziiert (Odds Ratio (OR) = 11,50, 95 %-KI 3,13–42,17; $p \leq 0{,}001$). Darüber hinaus schützte ein BMI ≥ 25 kg/m2 vor einer schweren Erkrankung (OR = 0,34, 95 %-KI 0,12–0,95; $p = 0{,}04$).

Originalarbeit 3

Body composition predictors of complicated Crohn's disease.

Barajas Ordonez F, Melekh B, Rodríguez-Feria P, Melekh O, Thormann M, Damm R, Omari J, Pech M, Surov A.

In letzter Zeit wurde intensiv erforscht, wie Veränderungen der Körperzusammensetzungsparameter sich auf das Auftreten von Komplikationen bei MC-Patienten auswirken. Diese Veränderungen können zu einer Zunahme der Krankheitsbelastung und einer Verschlechterung der Lebensqualität führen [65–67]. Es wurde herausgefunden, dass eine VAT-Hypertrophie den Entzündungsprozess verstärken kann [68]. Ein erhöhtes VAT/SAT-Verhältnis wurde als Risikofaktor für das Auftreten von Strikturen und Fisteln identifiziert [69]. Zudem wurde eine Verbindung zwischen Sarkopenie und längeren Krankenhausaufenthalten nachgewiesen [70]. Allerdings sind die bisherigen Studien zu diesem Thema noch begrenzt. Das Ziel unserer Untersuchung bestand daher darin, die Beziehung zwischen den Körperzusammensetzungsparametern und MC-Komplikationen einzuschätzen.

Es wurde eine retrospektive Bewertung von 114 Patienten durchgeführt, die mit MC diagnostiziert wurden und eine MRE durchgemacht hatten. Gemäß der Montreal-Klassifikation wurden die Patienten in eine Gruppe mit entzündlicher Erkrankung (n = 54) und eine Gruppe mit komplizierter Erkrankung (n = 60) eingeteilt. Die halbautomatische Beurteilung der Körperzusammensetzung und die qualitative Bewertung von CrF wurden durchgeführt.

Die Körperzusammensetzungsparameter unterschieden sich zwischen beiden Gruppen nicht hinsichtlich des Body-Mass-Index (p = 0,50), des gesamten Fettgewebeindexes (TATI) (p = 0,14), des subkutanen Fettgewebeindexes (SATI) (p = 0,17), des viszeralen Fettgewebeindexes (VATI) (p = 0,33), des VAT/SAT-Verhältnises (p = 0,77), des intramuskulären Fettgewebes (p = 0,64), des Skelettmuskelindexes (p = 0,22) und der Sarkopenie (p = 0,50). Es wurden 47 Strikturen, 18 Fisteln und 7 Abszesse identifiziert. Die Fisteln traten häufiger bei Patienten mit CrF (OR = 5,07, 95 %-KI 1,76–14,56; p=<0,001) und hohem VAT/SAT-Verhältnis (OR = 3,82, 95 %-KI 1,34–10,85; p = 0,01).

Originalarbeit 4

Diagnostic value of apparent diffusion coefficient of psoas muscles for evaluating complication in patients with Crohn's disease

Melekh B, Barajas Ordonez F, Melekh O, Flintrop W, Pech M, Surov A

Sarkopenie, ein fortschreitender und weitreichender degenerativer Verlust von Skelettmuskelmasse, tritt bei CED-Patienten hauptsächlich aufgrund von Mangelernährung durch eine langanhaltende entzündliche Darmerkrankung auf [71]. In einer bevölkerungsbasierten Studie wurde von Sharif et al. festgestellt, dass die Patienten mit Polymyositis und Dermatomyositis eine signifikant höhere Rate von CED aufwiesen [72]. Darüber hinaus weisen zahlreiche veröffentlichte klinische Fälle von Augen- oder Wadenmyositis bei MC-Patienten auf die Notwendigkeit einer weiteren Analyse von Muskelveränderungen mithilfe zusätzlicher Methoden hin, um unsere Kenntnisse der Pathomorphologie zu erweitern [73–76]. Im Jahr 2018 haben Surov et al. gezeigt, dass ADC als bildgebender Biomarker für myopathische Veränderungen bei Leberzirrhose genutzt werden kann [77]. Das Hauptziel dieser dieser Studie bestand darin, den Zusammenhang zwischen ADC der Skelettmuskulatur und der MC-Aktivität und dem MC-Verlauf als risikorelevante Faktoren zu analysieren.

Hierbei handelte es sich um eine retrospektive Studie mit 88 CD-Patienten, die sich MRE unterzogen. Auf der Höhe des dritten Lendenwirbels wurden die ADC-Werte des Psoas-Muskels sowie PMI auf beiden Seiten gemessen. Es wurde ein Vergleich von ADC und PMI von Patienten nach CD-Verhaltenstypen (Montreal-Klassifikation) und CD-Aktivität durchgeführt.

Unsere Studie umfasste 47 Männer und 41 Frauen mit einem Durchschnittsalter von 38,69 Jahren ± 14,4. Der signifikante Unterschied der ADC-Werte zwischen unkomplizierter Erkrankung (B1, n = 45) und komplizierter Erkrankung (B2 + B3, n = 43) mit Mittelwerten von 1,11 ± 0,19 (10-3*mm^2/s) bzw. 1,03 ± 0,10 wurde beobachtet (p = 0,02). Auch der ADC war bei nicht-strikturierenden Patienten (n = 51) signifikant höher als bei Patienten mit Strikturen (n = 37) (1,10 ± 0,18 bzw. 1,02 ± 0,11, p = 0,01). Bei der Beurteilung des PMI zeigten Patienten mit nicht penetrierender Erkrankung klinisch höhere Werte als Patienten mit penetrierender Erkrankung (5,71 ± 1,88 vs. 4,42 ± 1,55 cm^2/m^2, p = 0,10).

5. Diskussion

Die MRT-Enterographie spielt eine entscheidende Rolle bei der Diagnose und Behandlung von MC-Patienten. Diese Methode ermöglicht die Beurteilung des Entzündungszustandes der Darmwand und wird daher aktiv zur Analyse des Krankheitsverlaufs, der Komplikationen und des Therapieansprechens eingesetzt [51,78,79]. Angesichts der veröffentlichten Ergebnisse zur Akkumulationsfähigkeit von Gadolinium im Gehirn wird die Sicherheit dieser Methode jedoch aktiv diskutiert [54,55]. Eine Reihe neuerer Studien hat die Wirksamkeit der diffusionsgewichteten Bildgebung zur Beurteilung des pathologischen Prozesses bei MC-Patienten gezeigt [37,50,58,80–86]. Diese Arbeiten zeigten, dass die Verwendung von Diffusionsbildern und deren ADC-Karten es ermöglicht, nicht nur die klinische Aktivität des Prozesses, sondern auch die morphologischen Veränderungen zu bewerten. Allerdings gibt es trotz der zunehmenden Anzahl an Forschungsarbeiten immer noch kein klares Verständnis über die genaue Rolle von ADC und eine systematische Analyse der veröffentlichten Daten ist erforderlich. Dieses Problem wurde zum Ziel unserer ersten Arbeit, nämlich der Analyse der Rolle von ADC bei der Beurteilung der Krankheitsaktivität bei MC-Patienten.

In unserer 1. Studie identifizierten wir eine deutliche umgekehrte Korrelation ($p = -0,80$) zwischen ADC und CDAI. Dieser Zusammenhang ist von erheblicher Bedeutung für die klinische Praxis, da der CDAI als Goldstandard für die klinische Bewertung von MC-Patienten dient. Allerdings ist die Reproduzierbarkeit aufgrund erheblicher zwischenbeobachterabhängiger Fehler begrenzt [87]. In Anbetracht der engen Beziehung zwischen ADC und CDAI, wie in unserer Untersuchung festgestellt, deutet dies darauf hin, dass der ADC als alternative Methode zur klinischen Bewertung von Patientensymptomen verwendet werden kann.

Zudem identifizierten wir eine signifikante Beziehung zwischen ADC und MaRIA ($p = -0,66$). Eine prospektive Studie von Straksyte et al. mit einer umfangreichen Teilnehmerzahl ($n = 229$) wies eine ausgeprägte umgekehrte Korrelation zwischen ADC und den MaRIA-Score sowie Clermont-Score auf [88]. Angesichts der Ergebnisse des kumulativen Korrelationsindexes und prospektiver Daten könnte die ADC-Messung ein erhebliches Potenzial für die klinische Anwendung haben, mit einfacherer Reproduzierbarkeit im Vergleich zu MaRIA . In der Analyse morphologischer Veränderungen stellten wir eine deutliche Korrelation zwischen den ADC- und SES-CD-Werten fest ($r = -0,66$). Diese Ergebnisse decken sich mit den Befunden der Untersuchung von Buisson et al. [33], die eine Verbindung zwischen ADC und der Ausdehnung sowie Größe entzündlicher Geschwüre aufzeigte. Die Beurteilung

von entzündlichen und fibrotischen Veränderungen spielt eine entscheidende Rolle in der MC-Therapie, da sie weiterhin einer der Hauptgründe für Krankenhausaufenthalte und chirurgische Eingriffe bei MC-Patienten darstellt [85,86]. Lee et al. zeigten die Fähigkeit, mittels ADC zwischen fibrotischen und nicht-fibrotischen Veränderungen in der Darmwand zu differenzieren [84].

Die erhaltenen Ergebnisse legen die Hypothese nahe, dass ADC-Werte als wertvolle bildgebende Biomarker zur Beurteilung der Krankheitsschwere und morphologischer Veränderungen dienen könnten. Messungen des ADC könnten somit neben etablierten klinischen Bewertungen als diagnostischer Eckpfeiler für die Entscheidungsfindung in der Behandlung verwendet werden.

Mit dem Fortschritt neuer Methoden zur Analyse radiologischer Bilder, insbesondere der Anwendung halbautomatischer Techniken zur Segmentierung verschiedener anatomischer Strukturen, gewinnt die diagnostische Bedeutung von radiologischen Untersuchungen jedoch eine erweiterte Perspektive. Die MRT-Enterographie ermöglicht heute nicht nur die Beurteilung des Zustands der Darmwand, sondern auch die Bewertung des viszeralen und subkutanen Fettgewebes sowie der Skelettmuskulatur [89]. Diese Parameter werden bei Krebspatienten aktiv genutzt, um den Fortschritt des Tumorprozesses und seine systemischen Auswirkungen zu beurteilen. Angesichts des chronischen MC-Verlaufs und seiner direkten Auswirkungen auf Verdauungsprozesse könnten Analysen komplexer Parameter unserer Ansicht nach dazu beitragen, nicht nur die Diagnose, sondern auch die Behandlung dieser Patienten zu verbessern. Zusätzlich deutet das CrF-Auftreten, das im Kontext von MC entsteht und auf einen aggressiveren Verlauf des Entzündungsprozesses hinweist, darauf hin, dass die Analyse der Körperzusammensetzungsparameter durchaus machbar ist. Daher wurden in den beiden nachfolgenden Originalarbeiten (Originalarbeit 2 und 3) die Bewertung der Körperzusammensetzungsparameter und deren Vergleich mit CrF sowie der Zusammenhänge von Aktivität, Verlauf und Komplikationen von MC als Forschungsziele festgelegt.

Die 2. Originalstudie analysierte Körperzusammensetzungsparameter und CrF im Zusammenhang mit der MC-Aktivität, die anhand der MaRIA bewertet wird. Unsere Ergebnisse legen nahe, dass CrF signifikant mit einer schweren Erkrankung assoziiert ist (OR = 11,50, 95 %-KI 3,13–42,17; $p \leq 0,001$). Diese Ergebnisse stehen im Einklang mit früheren Studien von Althoff et al., die einen Zusammenhang zwischen CrF und dem komplexen MC-Verlauf festgestellt haben (OR = 3,5; $p \leq 0,5$) [64]. CrF ist definiert als eine lokale Zunahme des mesenterialen Fettgewebes, dessen mesenteriale Adipozyten eine bedeutende Quelle der

lokalen Produktion von CRP und proinflammatorischen Zytokinen darstellen [60,90]. In Übereinstimmung mit dieser Hypothese fanden wir bei der schweren Erkrankung signifikant höhere Serum-CRP-Spiegel im Vergleich zu den Gruppen mit leichter und mittelschwerer Erkrankung ($p \leq 0{,}001$). Diese Daten bestätigen frühere Studien [60,91]. Unserer Meinung nach bleibt die Schätzung von CrF begrenzt, da es bei der Bewertung der Prozessaktivität, insbesondere bei der Berechnung der MaRIA-Werte, nicht berücksichtigt wird. Außerdem wird CrF bei der Beurteilung von Körperparametern nicht ausreichend exakt eingeschätzt. Wie Suau et al. betonten, kann dies die Bewertung ihres Potenzials bei der Vorhersage des Therapieansprechens oder der Überwachung des MC-Verlaufs erschweren [92]. Rimola et al. fanden heraus, dass CrF ein negativer Prädiktor für die anhaltende Heilung entzündlicher Läsionen bei MC-Patienten war, die mit Tumornekrosefaktor-alpha (TNF-α)-Inhibitoren behandelt wurden [90]. Somit liefert unsere Arbeit Unterstützung für die weitere Bewertung von CrF in der MRT als Marker für einen schweren MC.

Bei der Analyse der Körperzusammensetzungsparameter zeigte sich, dass SATI in der Gruppe mit leichter bis mittelschwerer Erkrankung signifikant höher war als in der Gruppe mit schwerer Erkrankung ($p = 0{,}03$). In der univariaten Analyse war ein hoher SATI nicht signifikant mit einer schweren Erkrankung assoziiert (OR = 0,76, 95 %-KI 0,36–1,61; $p = 0{,}48$). Es ist bekannt, dass Fettleibigkeit zu einem signifikanten Anstieg des VAT und SAT führen kann [93]. In unserer Studie erwies sich ein BMI $\geq$ 25 kg/m2 als schützender Faktor gegen schwere Erkrankungen (OR= 0,34, 95 %-KI 0,12–0,95; $p = 0{,}04$). Diese Ergebnisse stimmen mit den Beobachtungen von Jain et al. überein, die berichteten, dass Fettleibigkeit und Übergewicht bei Kindern mit neu diagnostizierter chronischer Nierenerkrankung ein Jahr nach der Diagnose im Vergleich zu Kindern mit Normalgewicht nicht zu einer schlechteren Krankheitsaktivität führten [94]. Die Feststellung, dass adipöse Patienten mit chronischer Nierenerkrankung im Vergleich zu nicht-adipösen Patienten ein erhöhtes Risiko für postoperative infektiöse Komplikationen aufweisen, könnte auch durch die Tatsache erklärt werden, dass Adipositas ein Faktor ist, der zu Komorbiditäten wie Typ-2-Diabetes und Herz-Kreislauf-Erkrankungen beiträgt [95,96].

In unserer 3. Originalarbeit haben wir den Zusammenhang zwischen CrF, Körperzusammensetzungsparametern und dem Auftreten von Komplikationen bei MC-Patienten analysiert. Laut einer aktuellen Metaanalyse von Jiang et al. hatten Patienten mit CED und Adipositas ein erhöhtes Risiko für chirurgische Komplikationen (OR = 1,45; $p \leq 0{,}001$), insbesondere infektiöse Komplikationen (OR = 1,48; $p = 0{,}003$), im Vergleich zu Patienten

ohne Adipositas [97]. In der Gruppe der Patienten mit Übergewicht oder Adipositas wurde jedoch keine erhöhte Häufigkeit von Krankheitskomplikationen beobachtet (p = 0,56). Diese Ergebnisse stimmen mit der Erkenntnis anderer Autoren überein, dass der BMI an sich nicht mit dem Krankheitsverlauf assoziiert ist [98,99].

Die Unterteilung unserer Population nach SATI-Grenzwerten in Bezug auf Geschlecht (niedriger/normaler vs. hoher SATI) und (niedriger/normaler vs. hoher VATI) ergab keine Vorhersage für das Auftreten spezifischer Komplikationen (Fistel, Abszess oder Striktur). Unsere Daten legen nahe, dass VAT, VATI, SAT und SATI allein nicht ausreichen, um MC-Komplikationen vorherzusagen. Die erzielten Ergebnisse stimmen mit den von Erhayiem et al. durchgeführten Untersuchungen überein [68]. Sie fanden heraus, dass das durchschnittliche VAT/SAT-Verhältnis bei MC-Patienten, die Striktur- oder Fistelbildungskomplikationen aufwiesen, signifikant höher war als bei Patienten mit unkomplizierter Erkrankung (p = 0,001). In Bezug auf Abszesse konnten wir in der VAT/SAT-Analyse keinen statistischen Unterschied feststellen (OR = 1,48, 95 %-KI 3,14–6,97; p = 0,36). Dies könnte auf die geringe Anzahl von Patienten zurückzuführen sein, deren Krankheitsverlauf durch Abszesse erschwert wurde, da die MR-Enterographie nicht zu den Standarduntersuchungen für akute Bauchbeschwerden gehört. In unserer Kohorte war die Gesamtzahl der Patienten mit Abszessen gering (n = 7).

Bei der Untersuchung des Zusammenhangs zwischen CrF und Komplikationen fanden wir keinen signifikanten Unterschied zwischen Patienten mit Strikturkomplikationen im Vergleich zu Patienten ohne Strikturkomplikationen (p = 0,18). Der genaue Grund hierfür ist nicht offensichtlich. Es wurde zuvor berichtet, dass Veränderungen im Bindegewebe, einschließlich CrF, mit den lokalen Auswirkungen einer zugrunde liegenden chronischen Entzündung in Verbindung stehen [100]. In Übereinstimmung mit früheren Studien wurde in unserer Untersuchung kein spezifischer Unterschied zwischen entzündlichen und fibrösen stenotischen Veränderungen festgestellt, was darauf hindeutet, dass letztere stärker mit Veränderungen im Fettgewebe, einschließlich CrF, assoziiert sind [101]. Insgesamt trat CrF in unserer Studie bei Patienten mit komplizierten Erkrankungen häufiger auf als bei entzündlichen Erkrankungen (p = 0,11). Bei Patienten mit CrF waren Fistulierungskomplikationen häufiger als Strikturkomplikationen (OR = 5,07, 95 %-KI 1,76–14,56; p = <0,001). Die Feststellung, dass CrF bei Patienten mit Fisteln häufiger vorkam, ist nachvollziehbar, da CrF als schützende Reaktion beschrieben wurde. Dabei wandert mesenteriales Fettgewebe in Bereiche mit gestörter Darmbarriere, um die systemische Verbreitung potenziell schädlicher bakterieller Antigene zu verhindern, die durch die gestörte Barriere in den Darm gelangen könnten [102]. Zusätzlich können einige Bakterien direkt Endothelzellen und Adipozyten infizieren, was zu

ihrer Proliferation führt und letztendlich zur Entwicklung neuer Gefäße und mesenterialem CrF beiträgt [102,103]. Als Ergebnis können die Wände von Fisteln das Ergebnis von Neoangiogenese oder Lymphangiogenese in der Darmwand sein [103].

Zusammenfassend lässt sich sagen, dass die klinische Bedeutung unserer Daten darauf hinweist, dass die MRE-basierte Einteilung von CD-Patienten in Gruppen mit erhöhtem VAT/SAT sowie die radiologische Bewertung von CrF als potenzielle neue Prognosefaktoren für das Auftreten von Fistelkomplikationen in Betracht gezogen werden sollten.

In unserer 4. Originalarbeit haben wir die Bedeutung des ADC der Lendenmuskulatur als zusätzlichen Parameter untersucht, um Muskelveränderungen im Zusammenhang mit der Aktivität und dem Verhalten bei MC zu identifizieren. Angesichts der neuen Hypothese der "Darm-Muskel-Achse" besteht die Notwendigkeit, intramuskuläre Veränderungen zu bewerten, die aufgrund des systemischen Einflusses eines geringen Entzündungsgrades bei MC-Patienten auftreten können, um Formen mit ungünstiger Prognose frühzeitig zu erkennen [6,10]. Verschiedene frühere Studien haben die Wirksamkeit von DWI und ADC als nützliche klinische Instrumente zur Identifizierung intramuskulärer Störungen bestätigt [104–112]. Meyer et al. berichteten über signifikant höhere ADC-Werte in Muskeln bei Myositis und Myopathie im Vergleich zu nicht betroffenen Muskeln, was im Allgemeinen mit dem Auftreten von Muskelödemen verbunden war [104]. Weitere Veröffentlichungen von Meyer zeigten eine starke Korrelation zwischen den Ergebnissen des ADC und Elektromyographie bei Myositis, was die Möglichkeit bietet, den funktionellen Zustand der Muskeln widerzuspiegeln [112,113]. In unserer Studie ergab die ADC-Auswertung deutlich niedrigere Werte bei Patienten mit komplizierter Erkrankung im Vergleich zu unkomplizierter Erkrankung bzw. Strikturerkrankung im Vergleich zu nicht-strikturischer Erkrankung ($p=0,02$ bzw. $p=0,01$). Ran et al. beobachteten bei Patienten mit Myositis niedrigere ADC-Werte im Vergleich zu Kontrollpersonen mit nicht betroffenen Muskeln [110], was sie mit dem Auftreten zytotoxischer Reaktionen im Muskel erklärten. Eine alternative Hypothese von Dalaks et al. brachte die Diffusionsveränderungen mit einer Zunahme der Zellularität aufgrund der Migration von Entzündungszellen und verstärkten Entzündungsprozessen in Verbindung, was zu Ödemen und Nekrosen von Muskelfasern und einer erhöhten Zellzahl im Diffusionsraum für Wassermoleküle führt [114,115].

Zusammengefasst weisen unsere Ergebnisse auf eine erhebliche klinische Bedeutung der MR-Parameter bei MC hin. Erstens ist die Messung der ADC-Werte einfach und entspricht der Methode zur Bewertung zusammengesetzter Parameter des Körpers. Zweitens könnte der

statistische Unterschied der ADC-Werte zwischen Patienten mit kompliziertem und unkompliziertem Verlauf sowie zwischen penetrierenden und nicht-penetrierenden Formen dazu beitragen, Patienten mit schlechterer Prognose zu identifizieren. Drittens könnte eine weitere Analyse intramuskulärer Veränderungen auf der Grundlage von ADC-Messungen dazu beitragen, Patienten mit einer guten Prognose frühzeitig zu identifizieren.

5.1 Limitationen

Originalarbeit 1

Diese Arbeit weist manche Limitationen auf. Erstens wiesen viele der eingeschlossenen Studien retrospektiven Charakter auf. Zweitens gestaltete es sich als Herausforderung, die verschiedenen Altersgruppen kontinuierlich zu standardisieren, was zu erheblicher Heterogenität führte. Drittens wurden die erfassten Daten auf unterschiedlichen MRT-Scannern mit variierenden technischen Parametern (Magnetstärke, B-Werte und Erfassungszeit) aufgezeichnet. Zudem war die Vorbereitung der Patienten nicht einheitlich standardisiert, was jedoch die Vielfalt des klinischen Alltags widerspiegelt. Aufgrund der begrenzten Anzahl der an den Studien beteiligten Patienten konnten wir dies bedauerlicherweise nicht durch zusätzliche Teilanalysen angehen und waren daher nicht in der Lage, eine Metaanalyse oder Regressionsanalyse durchzuführen. Viertens variierte der Referenzstandard zur Beurteilung von Entzündungen in allen Studien, wobei einige chirurgische Proben und andere endoskopische Untersuchungen verwendeten. Fünftens wurde diese systematische Überprüfung nicht in einem Register festgehalten, was möglicherweise zu Verzerrungen bei der Datenerhebung geführt hat. Darüber hinaus wiesen einige unserer Untergruppen trotz zahlreicher eingeschlossener Studien eine geringe Patientenzahl auf.

Originalarbeit 2 und 3

Eine Einschränkung dieser Studien war das monozentrische Design und die retrospektive Methodik. Die anthropometrischen Messungen wurden aus den elektronischen Krankenakten extrahiert. Zudem waren die klinischen Daten zur medikamentösen Therapie bei MC unvollständig. MC-Patienten, die aufgrund akuter Komplikationen wie gastrointestinale Blutung, Hohlorganperforation oder Ileus notfallmäßig in der Klinik erschienen und in der Regel eine CT-Untersuchung als Akutdiagnostik benötigten, wurden möglicherweise nicht in die Studien eingeschlossen. Die Quantifizierung von Körperzusammensetzungsparametern aus MRT-Untersuchungen ist bisher kein standardisiertes Verfahren, und es gibt erhebliche Unterschiede hinsichtlich des Protokolls, der verwendeten Software und der

Normalisierungsfaktoren. Die Auswertung der Körperzusammensetzung sowie der MC-Komplikationen und -Aktivität im zeitlichen Verlauf oder zu verschiedenen Zeitpunkten der Erkrankung wurde in den vorliegenden Arbeiten nicht analysiert. Prospektive Studien könnten diese Fragestellungen näher beleuchten.

Originalarbeit 4

Es gibt mehrere Einschränkungen in dieser Studie, die berücksichtigt werden müssen. Die Studie war monozentrisch und hatte ein retrospektives Design. Informationen zur aktuellen Therapie waren unvollständig dargestellt. Es fehlte eine histologische Bestätigung intramuskulärer Veränderungen, was die Bestätigung oder Ablehnung einer Lendenmuskel-Myositis unmöglich machte. Nicht alle Patienten mit perforierenden Komplikationen unterzogen sich einer MRT; in einigen Notfällen war eine CT-Untersuchung erforderlich. Die Nachbeobachtungszeit für jeden Patientenscan musste standardisiert werden, was in der Analyse nicht berücksichtigt wurde.

6. Zusammenfassung

Diese Arbeit demonstrierte die Zweckmäßigkeit halbautomatischer Methoden zur Abschätzung der Körperzusammensetzungsparameter und des CrF während der MRT-Enterographie bei MC-Patienten. Die gewonnenen Ergebnisse können die Diagnose von Patienten deutlich verbessern und Risikofaktoren für einen schweren Verlauf und das Auftreten von Komplikationen beurteilen, die häufig eine stationäre Behandlung mit anschließender chirurgischer Behandlung erfordern.

In der 2. Originalstudie wurde ein deutlicher Zusammenhang zwischen CrF und einem schweren MC-Verlauf festgestellt (OR = 11,50, 95 %-KI 3,13–42,17; $p \leq 0,001$). Bei der Auswertung von MC-Komplikationen in der 3. Originalarbeit wurde ebenfalls eine Verbindung zwischen CrF und einem hohen VAT/SAT-Verhältnis mit dem Auftreten von Fisteln gefunden (OR = 5,07, 95 %-KI 1,76–14,56; $p < 0,001$; OR = 3,82, 95 %-KI 1,34–10,85; $p = 0,01$).

Des Weiteren wurde die Sinnhaftigkeit betont, diffusionsgewichtete Sequenzen und ADC-Karten in das Protokoll der MR-Enterographie einzubeziehen, wodurch der diagnostische Wert dieser Untersuchungsmethode erheblich gesteigert werden kann.

Unsere Metaanalyse (die 1. Originalarbeit) zeigt, dass ADC mäßige bis starke Assoziationen zwischen ADC und CDAI-, MaRIA- und SES-CD-Scores aufweist und daher als wichtiges Instrument für die CD-Krankheitsaktivität verwendet werden kann. Die Rolle des ADC bei der Beurteilung fibrotischer Veränderungen in der Darmwand ist jedoch begrenzt. ADC-Werte können akute Entzündungsreaktionen widerspiegeln, aber keine systemische Entzündung. Zusätzlich wurde bei der Messung des ADC der Lendenmuskulatur (die 4. Originalarbeit) beobachtet, dass die ADC-Werte bei MC-Patienten, insbesondere solchen mit einer Striktur, signifikant niedriger waren. Diese Befunde legen nahe, dass der ADC zur Identifikation von Patienten mit ungünstigem Krankheitsverlauf genutzt werden kann, insbesondere zur Unterscheidung zwischen komplizierten und unkomplizierten MC-Verläufen.

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8. Publikationen

8.1 Publikation 1.

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MAGNETIC RESONANCE

Apparent diffusion coefficient for assessing Crohn's disease activity: a meta-analysis

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Abstract

Purpose To analyze relationships betweenapparent diffusion coefficient (ADC) and activity parameters of Crohn's disease, e.g., length and wall thickness, CRP, FCP, MaRIA, CDAI, SES-CD, histologic inflammatory activity score, and the histological fibrotic score, based upon published data.

Materials and methods MEDLINE library, Scopus, and Embase databases were screened for association between ADC and activity parameters of Crohn's disease in patients with Crohn's disease up to Mai 2021. Overall, 21 studies with 1053 patients were identified. The following data were extracted from the literature: number of patients, correlation coefficients between ADC and length as well as wall thickness, CRP, FCP, MaRIA, CDAI, and SES-CD, inflammatory activity score, and fibrotic score. Associations between ADC and activity parameters were analyzed by Spearman's correlation coefficient. The studies' methodologic quality was evaluated by using the Quality Assessment of Diagnostic Studies (QUADAS 2) instrument, revealing a low risk of bias.

Results In the overall sample, the pooled correlation coefficient between ADC and CDAI was −0.8 (95% CI = [−0.94; −0.65]), between ADC and MaRIA −0.66 (95% CI = [−0.79; −0.53]). A strong association was observed between ADC and SES-CD with a pooled correlation of −0.66 (95% CI = [−0.87; −0.46]). The pooled sensitivity to discriminate between involved and non-involved bowel segments was 0.89, with an area under the curve of 0.89

Conclusions ADC showed strong inverse correlations with CDAI, MaRIA, and SES-CD scores. However, the role of ADC in assessing fibrotic changes in the bowel wall is limited. ADC can reflect acute inflammatory reactions but not systemic inflammation.

Key Points

- *ADC value can reflect acute inflammatory reactions but not systemic inflammation.*
- *ADC is inversely correlated with CDAI, MaRIA, and SES-CD.*
- *The role of ADC in assessing fibrotic changes in the bowel wall is limited.*

Keywords Crohn's disease · Magnetic resonance imaging · Diffusion-weighted imaging · Meta-analysis

Abbreviations

ADC	Apparent diffusion coefficient
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
DWI-MRE	Diffusion-weighted sequences
FCP	Fecal calprotectin
MaRIA	Magnetic resonance index of activity
MRE	Magnetic resonance enterography
SES-CD	Endoscopic activity score

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Introduction

Crohn's disease (CD) is one of the common chronic disorders in the industrialized world with an incidence of 3–20 cases per 100,000 and a wide spectrum of clinical manifestations [1–3]. Due to the varying pattern of CD, disease activity must be closely monitored. Severity of disease can be determined with quantitative or semiquantitative assessment of inflammation in the bowel [4].

Aside from laboratory, endoscopic, and enterographic examinations, magnetic resonance enterography (MRE) is the most important imaging modality for monitoring disease activity. It allows non-invasive investigation of the gastrointestinal tract and provides an assessment of inflammatory activity and potential complications in all bowel segments [5–9]. Current MR protocols include rapid MR sequences for data acquisition during a single breath-hold with minimal motion artefacts and rapid morphological sequences with a gadolinium-chelate-enhanced series [10]. However, with rising concerns about gadolinium retention in different organs, particularly the brain, the repeated application of gadolinium-based contrast agents is viewed critically [11, 12]. Therefore, alternative non-enhanced methods for repeated lifelong disease monitoring have gained relevance. MRI protocols usually include diffusion-weighted sequences (DWI-MRE), allowing for qualitative and quantitative assessment of random motion of water molecules in biological tissues. The use of DWI is recommended as an optional sequence for Crohn's disease by the European Society of Gastrointestinal and Abdominal Radiology in the latest consensus statements [13]. DWI could therefore potentially replace the contrast-enhanced sequences with comparable diagnostic power [6].

Choi et al [14] showed in a meta-analysis that accuracy and diagnostic strength of DWI-MRE in assessing bowel inflammation were overestimated in some studies. The correlation of DWI-derived apparent diffusion coefficient (ADC) with disease activity produced heterogeneous results and clinical relevance of quantitative ADC measurements could not be established due to the limited number of studies available at the time. With a growing interest in DWI-MRE and ADC in CD patients in recent years, this paucity has been largely cleared. A recent meta-analysis involving nine studies with pediatric patients with inflammatory bowel disease reported a sensitivity and specificity of DWI-MRE of 0.93 and 0.95, respectively [15]. In the meta-analysis by Choi et al [14], the data was based mostly on studies explaining the diagnostic value of DWI images and not the quantitative ADC value. Moreover, the published data has been increasingly growing since then, necessitating an updated analysis. To our knowledge, no systematic evaluation of the associations of ADC values with inflammation and fibrosis scores in CD has been performed in an adult population [16–29].

The aim of the present meta-analysis was to analyze the role of ADC in assessing disease activity in patients with CD.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the literature search [30].

Literature search

MEDLINE library, Scopus, and Embase online databases were checked to identify studies for associations between ADC and different activity parameters of Crohn's disease up to Mai 2021 using the following search criteria: "(Crohn) OR (inflammatory bowel disease) OR (IBD) AND (DWI) OR (diffusion weighted imaging) OR (ADC) OR (apparent diffusion coefficient)." Only papers written in English were included.

Inclusion criteria

The first primary endpoint of the meta-analysis was the reported correlation between quantitative ADC measurements and activity parameters of Crohn's disease. The second primary endpoint was the reported diagnostic abilities of ADC values for discrimination purposes of acute inflammation and fibrosis.

Studies (or subsets of studies) were included if they satisfied the following criteria:

1. Patients with Crohn's disease (based on standard clinical, endoscopic, imaging, and histologic criteria);
2. Patients, who underwent MR enterography with DWI sequence quantified by ADC values;
3. Correlation coefficient between ADC and activity parameters of Crohn's disease;
4. Receiver operating characteristic analysis with reported sensitivity, specificity, and area under the curve (AUC) for the discrimination analysis between involved and non-involved bowel segments.

Exclusion criteria

Exclusion criteria were as follows:

1. Systematic review;
2. Case reports;
3. Conference abstracts, letter, editorials, meta-analysis, guidelines;
4. Non-English language;
5. Studies that analyzed patients with colitis ulcerosa or colitis ulcerosa and Crohn's disease together.

Two readers (A.S. with 18 years of experience in radiology and B.M. with 9 years of experience in radiology)

independently evaluated all articles and studies. In cases of disagreement, a third observer (H.J.M. with 6 years of experience) was consulted to reach a decision in consensus.

Data extraction and quality assessment

Information was extracted on study characteristics (authors, year of publication, study design), demographic and clinical characteristics (sample size, male to female ratio, patient age), activity parameters, and correlation coefficients between ADC and activity of Crohn's disease. The activity parameters included wall thickness and length, fecal calprotectin (FCP) and C-reactive protein (CRP), a magnetic resonance index of activity (MaRIA) and Crohn's disease activity index (CDAI), endoscopic activity score (SES-CD), histologic inflammatory activity score, and also the histological fibrosis score.

In accordance with a wide spectrum of different activity parameters of Crohn's disease, we divided all data into subgroups for assessing the correlation with ADC: (1) studies with an investigated correlation between ADC and morphological changes such as length and wall thickness; (2) ADC and laboratory parameters such as FCP and CRP; (3) ADC and activity indices: MaRIA and CDAI; and (4) ADC and SES-CD, histologic inflammatory activity score, and the histological fibrosis score (Fig. 1).

For the present meta-analysis, our search criteria identified 1514 articles. Duplicate records, review articles, case reports, meta-analyses, non-English publications, and articles which were not within the field of interest were excluded (n = 1464) (Fig. 2). As a next step, full-text reviews of the remaining papers (n = 50) were performed. Thereafter, 26 articles were excluded, because they were not in the field of interest and did not contain an analysis of the correlation between ADC and Crohn's disease activity. Therefore, a total of 21 studies were involved in the analysis (Fig. 1) [16, 18–29, 31–38].

The methodologic quality of the studies was evaluated by using the Quality Assessment of Diagnostic Studies (QUADAS 2) instrument [39]. The following parameters were assessed for low, moderate, or high risk of bias: flow and timing, reference standard, index test, and patient selection.

Data synthesis and analysis

The correlations between ADC and activity parameters of Crohn's disease were calculated by Spearman's correlation coefficient. The reported Pearson's correlation coefficient was recalculated into Spearman's correlation coefficients according to the previous description [40].

The statistical analysis of the meta-analysis was calculated in program RevMan 5.3 (computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The heterogeneity was determined by using the inconsistency index I^2 [41, 42] and defined as not important with a value of index between 0 and 40%; moderate—between 30 and 60%; substantial heterogeneity—50–90%; and finally considerable—more than 75% [43]. DerSimonian and Laird's [44] random-effects models with inverse-variance weights were estimated without any further correction.

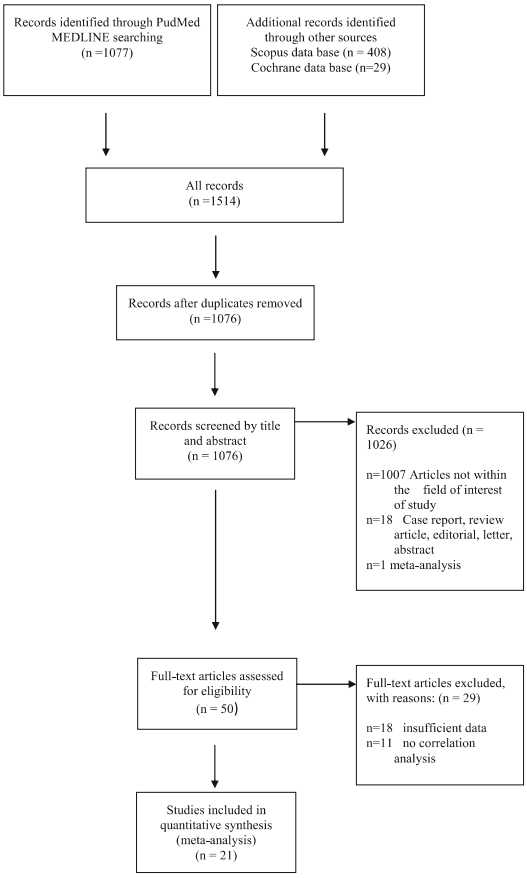

Fig. 1 Flowchart of the data acquisition

Results

The 21 included studies comprised 1053 patients, of which 496 patients (47%) were female and 577 male (53%). There were 11 (52%) prospective and 10 (48%) retrospective studies. The size of the study population ranged from 20 to 229 patients with an average age of 26.5 years. Three studies reported results on pediatric patients [16, 37, 38], whereas the

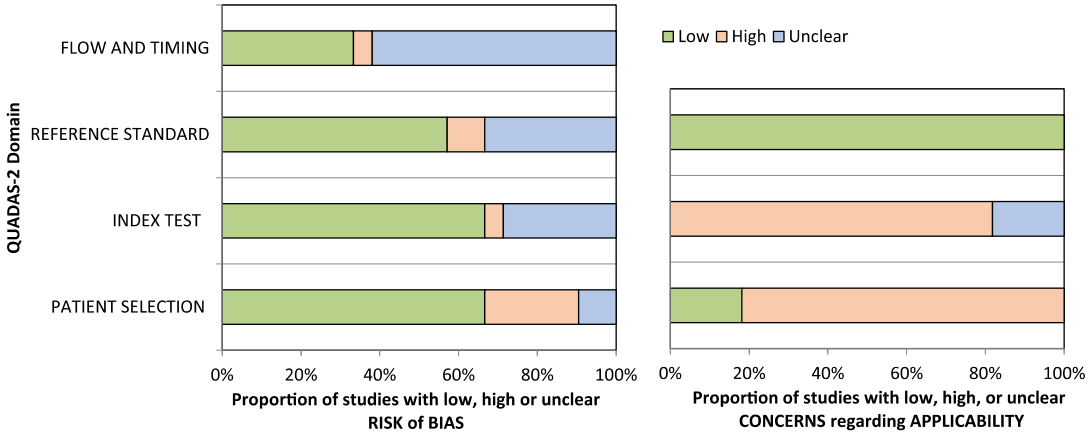

Fig. 2 QUADAS-2 quality assessment of the included studies. Most studies showed an overall low potential for sources of bias

other studies only investigated adult study populations. Detailed characteristics of all studies are shown in Table 1.

The QUADAS-2 assessment revealed an overall low to moderate risk of bias in the included studies. The reference standard for inflammation differed between studies as some studies used histopathological assessment and some only clinical severity, which can result in bias. The patient selection can be considered relatively free from bias, as only three studies included pediatric patients with inherent differences from the adult population. Across studies, ADC values were

Table 1 Characteristics of included studies

Authors	Year	Study design	Patients, *n*	Males:females	Age, mean	Tesla strength	Parameters
Abd-El Khalek Abd-Alrazek et al [25]	2018	Retrospective	72	40:32	30.9	1.5 T and 3 T	Wall thickness, MaRIA
Buisson et al [34]	2013	Prospective	31	11:20	26	1.5 T	MaRIA
Buisson et al [33]	2015	Prospective	44	21:23	27.9	1.5 T	SES-CD
Caruso et al [20]	2020	Retrospective	30	18:12	45.6	1.5 T	Histological inflammatory score, fibrosis score
Caruso et al [36]	2014	Retrospective	55	36:19	41	1.5 T	CRP, MaRIA, FCP, SES-CD
Cheng et al [27]	2019	Retrospective	51	37:14	29	3 T	SES-CD, MaRIA
Dillman et al [16]	2016	Prospective	28	17:11	15.3	3 T	Wall thickness, length, CRP, FCP
Du et al [21]	2021	Prospective	31	18:13	33	3 T	Histological inflammatory score, fibrosis score
Hectors et al [29]	2019	Prospective	27	18:9	42	1.5 T and 3 T	CRP, wall thickness, length, MaRIA
Klang et al [22]	2017	Retrospective	56	30:26	26	1.5 T	FCP, CRP
Li et al [23]	2017	Retrospective	43	27:16	26.8	3 T	SES-CD
Li et al [35]	2015	Prospective	47	29:18	27.9	3 T	CDAI
Li et al [28]	2019	Prospective	30	13:17	32.5	3T	Histological inflammatory score, fibrosis score
Li et al [24]	2018	Prospective	31	19:12	32.4	3 T	Fibrosis score
Neubauer et al [38]	2013	Retrospective	60	24:36	16	1.5 T	Wall thickness
Ream et al [37]	2013	Retrospective	46	23:23	14.3	1.5 T	Wall thickness, length
Strakšytė et al [18]	2020	Prospective	229	124:125	35.4	1.5 T	MaRIA
Tielbeek et al [32]	2014	Prospective	20	8:12	38	3 T	Fibrosis score
Wu et al [19]	2020	Retrospective	48	32:16	33.8	3 T	CDAI
Zhang et al [26]	2019	Prospective	24	14:10	30	3 T	Fibrosis score
Zhu et al [31]	2016	Prospective	50	18:32	32.3	3 T	CRP

measured as ADCmean values within a region of interest (ROI) of the inflamed bowel segment.

Correlations between ADC and MR morphological changes

In 2 studies including 74 patients, data about relationships between ADC and extent of bowel affection were reported. The pooled correlation coefficient between these parameters was −0.06 (95% CI = [−0.39, 0.28]), $p = 0.74$, heterogeneity $\tau^2 = 0.06$ ($p = 0.04$), $I^2 = 69\%$, test for overall effect $Z = 0.33$ (Fig. 3a). Associations between wall thickness and ADC were analyzed in 5 studies comprising 233 patients. The pooled correlation coefficient was −0.43 (95% CI = [−0.65; −0.22]), $p < 0.00001$, heterogeneity $\tau^2 = 0.04$ ($p = 0.002$), $I^2 = 76\%$, test for overall effect $Z = 3.92$ (Fig. 3b).

Correlation between ADC and disease activity scores

In 6 studies with 465 patients, a strong association between ADC and MaRIA was shown with a pooled correlation coefficient of −0.66 (95% CI = [−0.79; −0.53]), $p < 0.000001$, heterogeneity $\tau^2 = 0.02$ ($p < 0.0001$), $I^2 = 83\%$, test for overall effect $Z = 10.15$ (Fig. 4a).

Correlations between ADC and CDAI were reported in 2 studies (95 patients). The pooled correlation coefficient was −0.8 (95% CI = [−0.94; −0.65]), $p < 0.000001$, heterogeneity $\tau^2 = 0.01$ ($p = 0.06$), $I^2 = 71\%$, test for overall effect $Z = 10.73$ (Fig. 4b).

In addition, correlations between ADC and morphological parameters, like SES-CD, histological fibrotic score, and histologic inflammatory score, were evaluated (Fig. 5a–c).

In 4 studies with 193 patients, associations between ADC and SES-CD were analyzed. The pooled correlation coefficient was −0.66 (95% CI = [−0.87; −0.46]), $p < 0.000001$, heterogeneity $\tau^2 = 0.04$ ($p < 0.0001$), $I^2 = 88\%$, test for overall effect $Z = 6.40$ (Fig. 5a).

Correlations between ADC and histological fibrotic score were reported in 6 studies (166 patients). The pooled correlation coefficient was 0.49 CI (95% CI = [−0.61; −0.37]), $p < 0.000001$, heterogeneity $\tau^2 = 0.00$ ($p = 0.47$), $I^2 = 0\%$, test for overall effect $Z = 7.96$ (Fig. 5b).

In 3 studies (91 patients), relationships between ADC and histologic inflammatory score were investigated. The pooled correlation coefficient was −0.51 (95% CI = [−0.84, −0.18]), $p = 0.003$, heterogeneity $\tau^2 = 0.07$ ($p = 0.0004$), $I^2 = 82\%$, test for overall effect $Z = 3.00$ (Fig. 5c).

Correlation between ADC and blood inflammatory markers

Associations between ADC and CRP were shown in 5 studies with a total number of 216 patients and represented a weak pooled correlation—0.35 (95% CI = [−0.60, −0.09]), $p = 0.008$, heterogeneity $\tau^2 = 0.07$ ($p = 0.0004$), $I^2 = 81\%$, test for overall effect $Z = 2.64$ (Fig. 6a).

Association between ADC and FCP was reported in 3 studies (139 patients). The pooled correlation coefficient was 0.59 (95% CI = [−0.72, −0.47]), $p < 0.00001$,

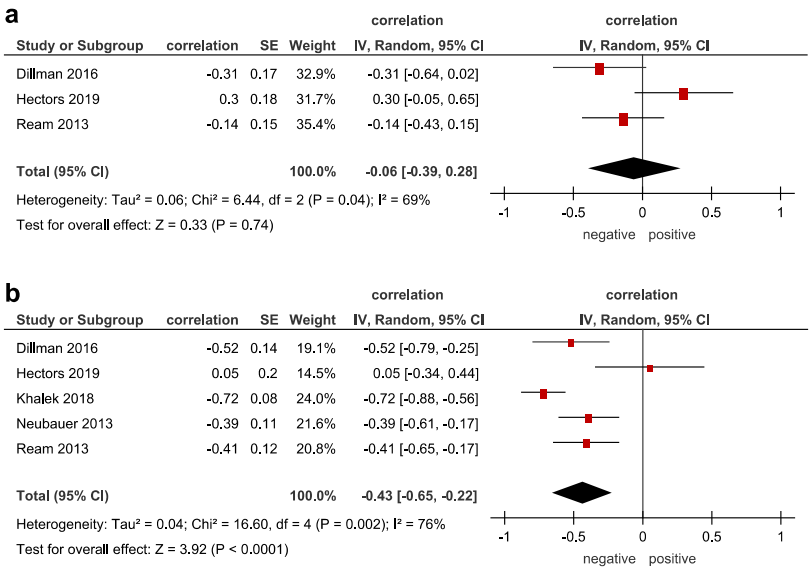

Fig. 3 Forest plots of correlation coefficients between (**a**) ADC and length of inflamed bowel wall, (**b**) ADC and thickness of inflamed bowel wall

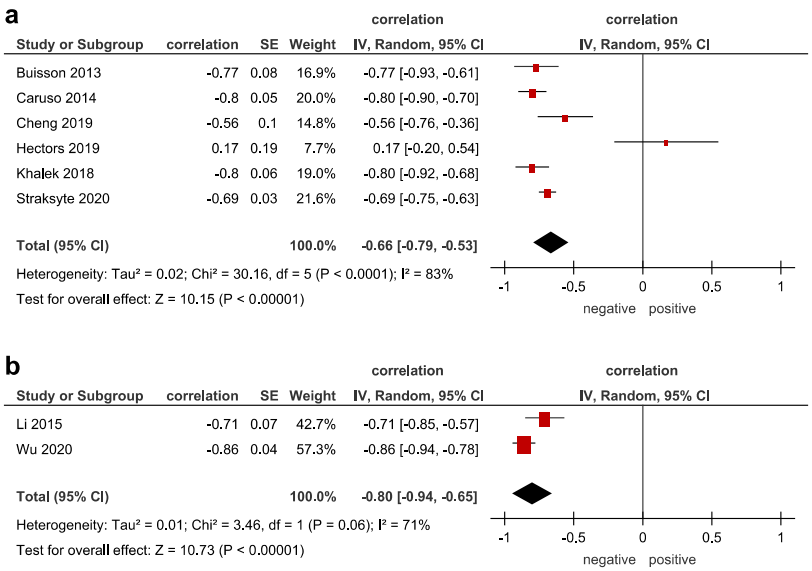

Fig. 4 Forest plots of correlation coefficients between (**a**) ADC and magnetic resonance index of activity, (**b**) ADC and Crohn disease activity index

heterogeneity $\tau^2 = 0.00$ ($p = 0.28$), $I^2 = 21\%$, test for overall effect $Z = 9.21$ (Fig. 6b).

Diagnostic accuracy of ADC values

The diagnostic value of ADC values was reported in 15 studies. The overall pooled sensitivity to discriminate between involved and non-involved bowel segments was 0.89, the specificity was 0.81, and the AUC was 0.89

For studies only investigating the discriminatory power between no/mild fibrosis to moderate/strong fibrosis, the AUC was 0.84, whereas for studies investigating only acute inflammation, the AUC was 0.91.

Discussion

The present meta-analysis showed inverse associations between ADC values and disease activity scores in patients with Crohn's disease. No strong correlation was found for the extent of bowel affection. MRE is performed routinely for most patients with CD due to its excellent diagnostic accuracy. In recent years DWI has become increasingly important in the assessment of bowel inflammation and may complement or potentially replace contrast-enhanced sequences [10]. Our results show that ADC measurements can be applied for disease monitoring in CD. To the best of our knowledge, this is the first comprehensive meta-analysis assessing the correlation of ADC with disease activity parameters in CD. ADC values could therefore potentially be employed as an imaging biomarker to guide treatment decisions. However, there is a clear need for proven threshold values and DWI method standardization.

A strong inverse correlation ($\rho = -0.80$) was observed in the correlation between ADC and CDAI. This finding may be significant in clinical practice. CDAI is used as a gold standard for the clinical evaluation of patients with CD. However, its reproducibility may be limited due to significant inter-observer error, even when performed by experienced physicians [45]. The strong association between ADC and CDAI could be a complement or even an alternative to symptom-guided evaluation. Our results can be considered robust as the total number of patients in the analyzed studies ($n = 95$) was large and reported results were standardized by age groups.

We also found a significant association between ADC and MaRIA score ($\rho = -0.66$). Strong associations were identified in all papers except for one work by Hectors et al [29], in which the long acquisition time of 9 min can be considered unfeasible. The prospective study by Straksyte et al [18], with a large number of patients ($n = 229$), showed a strong inverse correlation between ADC and MaRIA and Clermont indices. Considering the results of the cumulative correlation index as well as the prospective data, ADC measurements may have a strong potential for clinical practice and may be more easily reproduced than the MaRIA score.

We identified a strong correlation between ADC values and SES-CD ($\rho = -0.66$). This indicates the potential of ADC in assessing bowel inflammation. Our results are in line with the study by Buisson et al [33], showing a correlation between ADC and the depth and size of inflammatory ulcerations. The evaluation of inflammatory and fibrotic changes

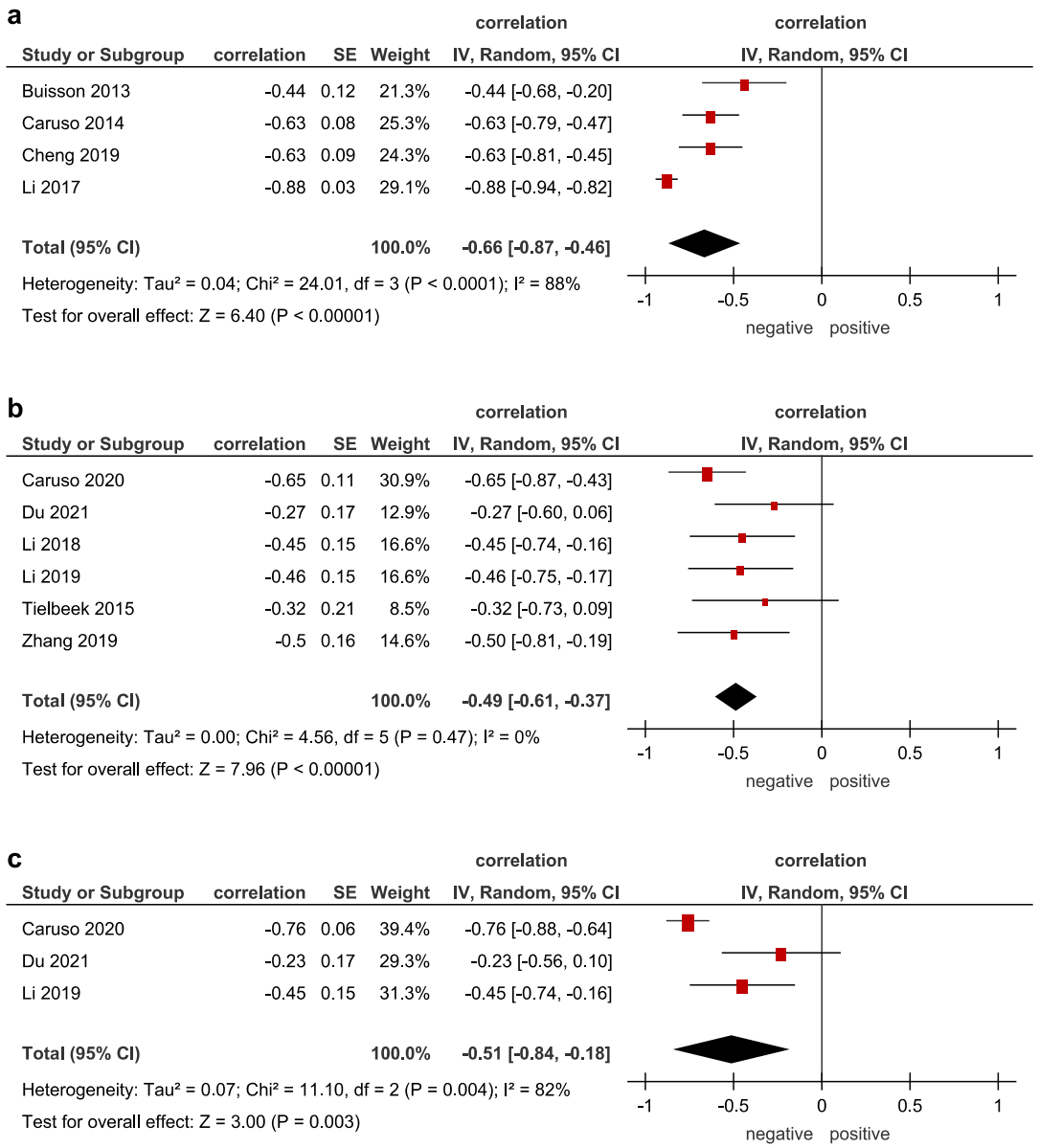

Fig. 5 Forest plots of correlation coefficients between (**a**) ADC and endoscopic activity score, (**b**) ADC and histological fibrotic score, (**c**) ADC and histologic inflammatory score

plays a crucial role in CD treatment [21]. Bowel fibrosis is one of the main causes of hospitalization and surgical resection in CD patients [26]. In the last years, a number of studies have been published investigating possible ways to assess and differentiate inflammatory changes from fibrotic histological alterations in bowel walls in patients with CD [20, 21, 24, 26, 28, 32]. Li et al [24] have reported that fibrotic and non-fibrotic bowel wall alterations could be differentiated by means of ADC. Also, mild inflammatory changes could be distinguished from severe ones. However, the ability of ADC to evaluate bowel fibrosis seems to decrease with increasing degrees of bowel inflammation [26].

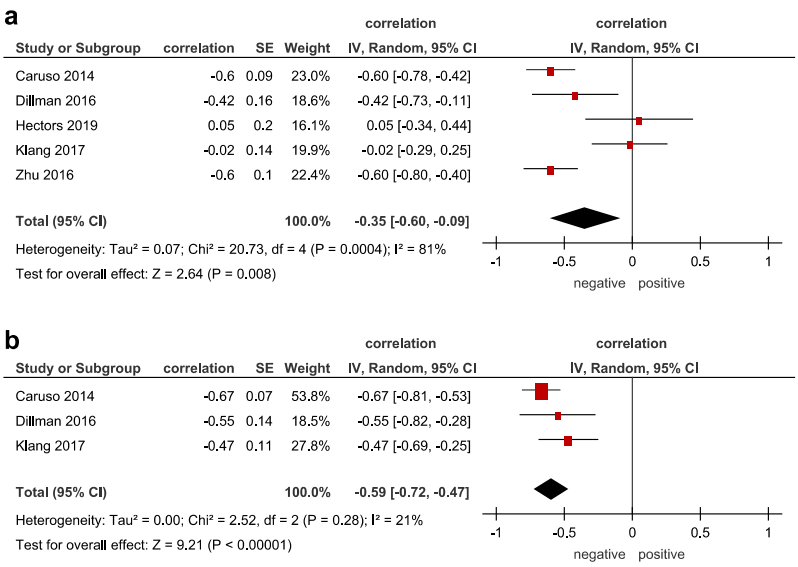

Fig. 6 Forest plots of correlation coefficients between (**a**) ADC and C-reactive protein, (**b**) ADC and calprotectin

Previously published studies reported a weak correlation between ADC values and length and thickness of bowel wall inflammation [16, 29]. Our analysis confirmed these results. Shortcomings of the available data, however, must be considered. First, only children were investigated in the included studies. Inflammatory bowel wall changes in children are not associated with fibrosis or fat accumulation, unlike in the adult population. In addition, no standardized measurement of the bowel length and thickness exists, particularly when bowel loops have a complex geometrical form or when bowel peristaltic is not sufficiently suppressed. Standardization of all images of different patients with many causes of wall thickening, like edema, fibrosis, or fat accumulation, or with different bowel distention or peristaltic suppression is challenging [46, 47]. Therefore, the correlation between these parameters and ADC may not be considered reproducible and reliable.

Regarding laboratory data, our findings also support previously published studies, in which Caruso et al [20], Dillman et al [16], and Zhu et al [31] each reported a weak inverse correlation between ADC and CRP. It remains unclear which inflammatory tissue alterations have the strongest impact on diffusion restriction. Zhu et al [31] hypothesized increased cell density in the bowel wall due to influx of lymphocytes, cell swelling, and increased viscosity due to granulomas and micro-abscess. All these processes also lead to a rise in CRP levels. The weak correlation indicates that ADC reduction allows the assessment of local inflammatory changes in the bowel but not of the systematic response, which is reflected by CRP. Thus, both parameters likely reflect distinctive aspects of disease activity.

Our results showed an inverse correlation between ADC and FCP (−0.59), confirming results reported by Dillman et al [16] and Klang et al [22]. FCP increases with inflammatory activity due to neutrophil migration to the gastrointestinal tract and is therefore a common marker of gut inflammation [48]. Restricted diffusion as expressed by ADC in combination with FCP may therefore improve disease monitoring, detect early subclinical inflammatory processes, and lead to better patient outcomes.

One outlier of the present analysis was the study by Hectors et al [29], which showed negative results for clinical parameters. One reason for this could be the employed IVIM technique in the study. The authors reported promising results for the differentiation between normal and abnormal bowel for IVIM-DWI parameters, being superior to ADC values alone. More data are needed to elucidate the potential of the IVIM-DWI technique.

The present results can lead to the hypothesis that ADC values can be used as a valuable imaging biomarker to assess disease severity, presumably better than morphological imaging. ADC measurements may serve as a diagnostic cornerstone for treatment decisions side by side with established clinical parameters like serological inflammation markers.

Our meta-analysis has some limitations. First, many of the included studies were retrospective in nature. Second, it was not possible to standardize the different age groups throughout, and as a result, the heterogeneity was substantial. Third, the acquired data was obtained on different MRI scanners with different technical parameters (magnetic strength, *b*-values, and acquisition time). In addition, the patients' preparation was not standardized. However, this reflects clinical routine with resulting heterogeneity. Unfortunately, we could not address this by further sub-analyses due to the small number of patients involved in the studies and were thus unable to perform a meta-

regression analysis. Fourth, the reference standard to assess inflammation was different throughout the studies. Some used surgical specimens for inflammation, whereas others used endoscopic evaluation. Fifth, this systematic review was not filed in a register, which can result in possible bias regarding the data collection. Furthermore, despite many included studies, some of our subgroups have a small number of patients.

In conclusion, our meta-analysis shows that ADC may be a significant tool for CD disease activity, albeit for selective parameters. We identified moderate-to-strong associations between ADC and CDAI, MaRIA, and SES-CD scores. However, the role of ADC in assessing fibrotic changes in the bowel wall is limited. ADC values can reflect acute inflammatory reactions but no systemic inflammation.

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Declarations

Guarantor The scientific guarantor of this publication is Prof. Alexey Surov.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was not required because no individual patient data were analyzed. Only aggregate patient data were analyzed in this meta-analysis.

Methodology
• retrospective
• meta-analysis

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Parameters of body composition and creeping fat are associated with activity of Crohn's disease

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ABSTRACT

Aim: This study aimed at assessing body composition parameters, creeping fat (CrF), and Crohn's disease's (CD) activity based on the Magnetic Resonance Index of Activity (MaRIA).
Methods: 114 CD patients who underwent magnetic resonance enterography (MRE) between June 2010 and April 2020 were retrospectively assessed. The semi-automated body composition segmentation, the qualitative evaluation of CrF, and MaRIA were performed. Based on their MaRIA score, patients were divided into two groups: mild-to-moderate disease (MaRIA <11, $n = 50$) and severe disease (MaRIA ≥11, $n = 64$). MRE parameters were analyzed between both groups. Patients were dichotomized according to body composition categories and the presence of CrF. Univariate regression analyses were performed to investigate the association between dichotomized variables and severe disease. Significant variables were incorporated into the multivariate logistic regression model.
Results: The severe disease group exhibited higher serum C-reactive protein (CRP) levels compared to the mild-to-moderate disease group ($p \leq 0.001$). In the mild-to-moderate disease group, a higher proportion of patients had a body mass index (BMI) ≥ 25 (kg/m^2) (32.0%) compared to the severe disease group (16.5%) ($p = 0.04$). The subcutaneous adipose tissue index (SATI) was significantly higher in the mild-to-moderate disease group ($p = 0.04$). The visceral to subcutaneous adipose tissue (VAT/SAT) ratio tended to be higher in the severe disease group ($p = 0.09$). There was no significant difference between both groups regarding total adipose tissue index (TATI) ($p = 0.10$), visceral adipose tissue index (VATI) ($p = 0.51$), intramuscular adipose tissue index (IMATI) ($p = 0.38$), skeletal muscle index (SMI) ($p = 0.83$), and sarcopenia ($p = 0.75$). In the multivariate analysis, CrF was significantly associated with severe disease (odds ratio [OR] 11.50, 95% confidence interval [CI] 3.13–42.17; $p \leq 0.001$). Additionally, a BMI ≥ 25 (kg/m^2) was protective against severe disease (OR: 0.34, 95% CI 0.12–0.95; $p = 0.04$).
Conclusion: CrF is significantly associated with CD activity.

1. Introduction

Growing evidence suggests that altered body composition parameters can affect the quality of life, postoperative complications, disease activity, and behavior in CD patients [1,2]. In 2015, Büning et al. claimed that CD patients with stricturing and fistulizing complications had a high VAT/ total fat mass (FM) ratio ($p = 0.067$) [3]. In 2017, Holt et al. identified high VAT as an independent risk factor for endoscopic recurrence of CD after surgery (OR 2.1, $p = 0.012$) [4]. In the same year, Cravo et al. identified a significant association between muscle attenuation (MA), visceral obesity, and CD complications (OR 0.81, $p = 0.002$ and OR 26.1, $p = 0.02$, respectively) [5].

CrF has been described as an expansion of the adipose tissue from the mesentery towards the intestine and is thought to create a reactive immunological zone around the inflamed intestine [6]. In 2019, Althoff et al. recognized that CrF assessed by magnetic resonance imaging (MRI)

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was independently associated with a complicated course of CD (OR 3.5, $p \leq 0.5$) [7].

CD has been traditionally associated with weight loss, which increased the risk of malnutrition [8,9]. Nevertheless, the prevalence of obesity among inflammatory bowel disease (IBD) patients is increasing, ranging between 15% and 40% [10]. In 2020, Jiang et al. asseverated that obese IBD patients have an increased risk of surgical compilations compared to nonobese patients (including overweight) (OR = 1.45, $p \leq 0.001$) [8].

According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is defined as a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes and mortality [11]. The prevalence of sarcopenia in CD is also high, reaching up to 60% [9]. In 2020, Erős et al. found that sarcopenia is an independent predictor of the rate of surgery in CD patients [12]. In 2021, Zhou et al. found that changes in CD activity assessed by the 5-point MRE classification were negatively correlated with SMI changes but positively correlated with the VAT to total adipose tissue (TAT) ratio (each, $p \leq 0.001$) [13].

Endoscopic scores are considered to be the gold standard for measuring CD activity [14]. The radiological assessment is essential for the evaluation of intra- and extraluminal complications, as endoscopy is limited to the evaluation of the mucosa [15,16]. Several studies have focused on developing MRE-based indices for the quantification of active CD disease [15]. In 2021, Ahmad et al. claimed that MaRIA is the most sensitive and specific MRI method for assessing CD activity [17]. The MaRIA score comprises several MRE features, which were found to be independent predictors of active endoscopic disease [15]. Studies regarding the influence of body composition predictors of CD activity measured by MRE-based indices, particularly MaRIA are scarce [13,18]. Besides, the MaRIA score does not include mesenteric fat alterations and CrF. This study aimed at retrospectively assessing body composition parameters and CrF on opportunistic MRE scans as predictors of CD's activity based on the MaRIA score.

2. Methods

2.1. Setting and participants

This was a monocentric study approved by the institutional review board (Nr. 145/21), Ethics Committee, Otto-von-Guericke University, Magdeburg, Germany. Patients with confirmed CD, who underwent MRE in the University Clinic for Radiology and Nuclear Medicine (University Hospital Magdeburg) between June 2010 and April 2020, were retrospectively assessed. A search of MRI scans of CD patients was performed using the picture-archiving and communication system (PACS) viewing station (INFINITT Healthcare, Seoul, South Korea). Clinical data was extracted from medical records using the internal database (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Germany). The clinical data included gender, age at the baseline and at onset, anthropometric measurements, current CD drug therapy, current smoking status, previous abdominal surgery, and C-reactive protein levels. The age at onset was documented according to the Montreal classification as follows: A1, <16 years; A2, between 17 and 40 years; and A3, over 40 years [19].

The inclusion criteria were: (a) first MRE chronologically available and (b) anthropometric data available. The exclusion criteria were: (a) MRI of the pelvis and (b) incomplete MRE data or technical difficulties. Overall, 437 MRI scans were identified. Two hundred thirty-five patients did not meet the inclusion criteria. Out of 184 eligible patients (MRE scans), 70 were excluded due to examination of the pelvis, incomplete MRE data, or technical difficulties. The final population comprised 114 patients.

2.2. MRE technique

The MRE protocol included fasting overnight. On the day of the examination 1200 mL of 2.5%, sorbitol in small aliquots over 4 h were orally ingested [20]. Additionally, the inhibition of intestinal motility was induced by applying intravenously 20 mg/mL of N-butylscopolamine (Buscopan, Boehringer Ingelheim, Germany). A gadolinium-based MRI contrast agent (Gadovist, Bayer Vital, Leverkusen, Germany) was administrated as an intravenous bolus injection at approximately 0.1 mL/kg. Each MRE scan was performed on a 1.5 Tesla MRI scanner (Intera, Philips Medical Systems, Best, the Netherlands) with the patient lying supine. The MRE sequences are shown in the Supplementary Table 1.

2.3. Assessment of complications, creeping fat, and MaRIA score

Each MRE was assessed by two radiologists, one senior resident with 9 years of experience and a senior staff radiologist with >18 years of experience. For each scan, the following aspects were evaluated: (a) CrF, defined as fatty deposition along the mesenteric border of inflamed bowel segment, (b) visible small bowel stricture, (c) presence of a fistula or an abscess [20–22]. The disease behavior was categorized based on the Montreal classification as follows: non-stricturing, non-penetrating (B1), stricturing (B2), and penetrating (B3) [19].

In this study, the simplified and segmental MaRIA score was used. It was calculated by the formula: 1.5 x wall thickness (mm) + 0.02 x relative contrast enhancement (RCE). RCE was previously calculated by the formula, RCE = [wall signal intensity (WSI) post gadolinium- WSI pregadolinium / (WSI pregadolinium)] x 100 x [standard deviation (SD) noise pregadolinium/ SD noise postgadolinium). SD noise pre- and postgadolinium refers to the average of three standard deviations (SD) of the signal intensity measured outside the body before and after the administration of gadolinium, respectively. Based on their MaRIA score, patients were divided into two groups mild-to-moderate disease (MaRIA <11) and severe disease (MaRIA≥11) [15].

2.4. Body composition analysis

Body composition analysis was performed at the L3 inferior endplate level (Fig. 1). The cross-sectional area (CSA) of TAT, SAT, VAT, skeletal muscle tissue (SMT), and intramuscular adipose tissue (IMAT) in square centimeters on the basis of pixel count were measured on MRE scans using the semi-automated segmentation tool, AsanJ-Morphometry (Asan Image Metrics, Seoul, Korea) [23]. Muscle and adipose tissues were separated using thresholds for the signal intensity on precontract T1-weighted MRE scans with a value of >350 signal intensity (SI) and < 750 SI for adipose tissue, and > 100 SI and < 350 SI for muscle.

2.5. Body composition categories

The BMI was determined by using the formula [weight (kg)/height squared (m^2)]. BMI categories were as follows: (a) underweight (<18.5 kg/m^2), (b) normal weight (18.5–24.9 kg/m^2), and (c) overweight and obesity (≥ 25.0 kg/m^2) [24]. Due to the small sample size, patients of the latter category were not further subclassified. For optimal stratification of our population regarding the body composition parameters assessed by MRE, the patients were classified according to sex-specific values. Sarcopenia was measured in terms of skeletal muscle index (SMI). The SMI was calculated by dividing the SMT (cm^2) by height squared (m^2). The SMI cut-off values of sarcopenia for men were: (a) 43 (cm^2/m^2) under a BMI of 25 (kg/m^2) and (b) 53 (cm^2/m^2) over a BMI of 25 kg/m^2; and for women was 41 (cm^2/m^2) [24]. TATI, SATI, VATI, and IMATI, were calculated by dividing TAT (cm^2), SAT (cm^2), VAT (cm^2), and IMAT (cm^2) by the height squared (m^2), respectively. The cutoff values for the classification of SATI (low- vs. high SATI) were 40 (cm^2/m^2) for men and 30 (cm^2/m^2) for women; and of VATI (low- vs. high

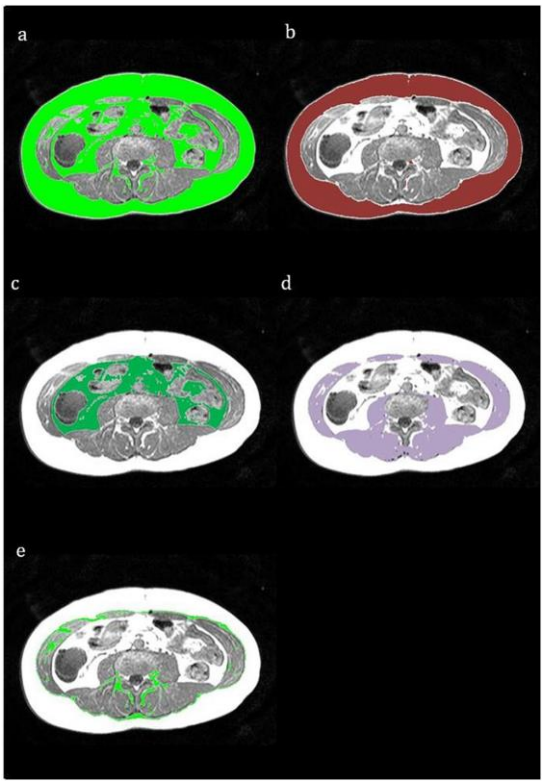

Fig. 1. Body composition segmentation.
Cross-sectional area (CSA) measurements at the L3 inferior endplate level. a. Total adipose tissue (TAT). b. Subcutaneous adipose tissue (SAT). c. Visceral adipose tissue (VAT). d. Skeletal muscle tissue (SMT). e. Intramuscular adipose tissue (IMAT).

VATI) 44.0 (cm^2/m^2) for men and 35 (cm^2/m^2) for women. The cutoff values of VAT/SAT ratio (low- vs. high VAT/SAT ratio) were 1.08 for men and 0.86 for women [24,25]. To the best of our knowledge cut-off values for IMATI have not been established.

2.6. Statistical analysis

Continuous variables are shown as mean (*M*) and *SD*. Continuous variables were compared between groups of mild-to-moderate disease and severe disease using the Student's *t*-test. Categorical variables were compared between both groups using the chi-squared test or Fisher's exact test. Patients were dichotomized based on the above-mentioned body composition categories, CrF, age, and sex. Univariate regression analyses were performed to investigate the association between dichotomized variables and severe disease (MaRIA score $\geq$ 11). Significant variables were incorporated into the multivariate logistic regression model. OR are presented together with a 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. Patient characteristics

The patient characteristics for the total population are summarized in Table 1. The mean age of the mild-to-moderate disease and severe disease group was 40.36 ± 18.5 and 37.52 ± 13.7 years, respectively. More than half of all patients were male (52.6%) in both groups. The B1 behavior was more common in the mild-to-moderate disease group compared to the severe disease group patients ($p \leq 0.001$). The complicated behavior (B2 or B3) was the most common in the severe disease group (65.6%) compared to the mild-to-moderate disease group (36%) ($p \leq 0.001$). The current treatment with corticosteroids tended to be more common in the severe disease group ($p = 0.08$). C-reactive protein levels were significantly higher ($p \leq 0.001$) in the severe disease group. There was no significant difference in disease duration, age of onset, active cigarette smoking, and previous abdominal surgery between both groups. In the mild-to-moderate disease group, a higher proportion of patients had a BMI $\geq$25 (kg/m^2) (32.0%) compared to patients in the severe disease group 15.6% ($p = 0.04$). This difference was statistically significant ($p = 0.04$).

3.2. Comparison of body composition parameters and creeping fat between mild-to-moderate disease (MaRIA < 11) and severe disease (MaRIA ≥ 11)

Body composition parameters and CrF distribution are listed in Table 2. There was no significant difference between both groups regarding TAT ($p = 0.12$), TATI ($p = 0.10$), VAT ($p = 0.57$), VATI ($p = 0.51$), IMATI, ($p = 0.38$), SMT ($p = 0.57$), and SMI ($p = 0.83$). The VAT/SAT ratio tended to be higher in the severe disease group ($p = 0.09$). SAT and SATI were significantly higher in the group of severe disease ($p = 0.04$ and $p = 0.03$, respectively). Patients in the severe disease group had a significantly higher proportion of CrF (38.8%) compared to the mild-to-moderate disease group (6.3%) ($p \leq 0.001$). Sarcopenia was identified

Table 1
Patient characteristics ($n = 114$), groups of mild-to-moderate disease (MaRIA <11) and severe disease (MaRIA ≥11).

	MaRIA <11 ($n = 50$), n (%)	MaRIA ≥11 ($n = 64$), n (%)	*p*-value
Male	26 (52.0)	34 (53.1)	0.90
Age at baseline (years)	40.36 ± 18.5	37.52 ± 13.7	0.35
Disease duration (years)	12.10 ± 15.3	8.83 ± 7.67	0.14
Age at diagnosis (years)	28.26 ± 14.9	28.69 ± 13.3	0.87
A1	12 (24.0)	12 (18.8)	0.50
A2	29 (58.0)	40 (62.5)	0.63
A3	9 (18.0)	12 (18.8)	0.92
Disease behavior			
B1	32 (64.0)	22 (34.4)	<0.001
Complicated (B2 or B3)	18 (36.0)	42 (65.6)	<0.001
Current drug therapy[+]			
Corticosteroids	10 (20.0)	26 (40.6)	0.08
Biological therapy	9 (18.0)	13 (20.3)	0.85
Immunomodulator	9 (19.0)	16 (25.0)	0.71
5-aminosalicylic acid therapy	4 (8.0)	10 (15.6)	0.41
Active cigarette smoking	7 (14.0)	6 (9.4)	0.44
Previous abdominal surgery	27 (54)	26 (40.6)	0.16
Body mass index (BMI) (kg/m^2)	23.33 ± 5.2	21.79 ± 4.1	0.09
BMI <18.5 kg/m^2	9 (18.0)	11 (17.2)	0.91
BMI 18.5–24.9 kg/m^2	25 (50.0)	43 (67.2)	0.06
BMI ≥ 25 kg/m^2	16 (32.0)	10 (15.6)	0.04
C-reactive protein levels (>5 ng /mL)	32 (64.0)	56 (87.6)	<0.001

Continuous variables are reported as median value ± standard deviation.
CD, Crohn's disease.
[+] Current Therapy information was available for 99 patients only.

Table 2
Comparison of body composition measurements and creeping fat between mild-to-moderate disease group (MaRIA <11) and severe disease group (MaRIA ≥11), ($n = 114$).

Body composition predictors	MaRIA <11 ($n = 47$), n (%)	MaRIA ≥11 ($n = 67$), n (%)	*p*-value
TAT (cm^2)	241.53 ± 177.0	195.29 ± 117.6	0.12
TATI (cm^2/m^2)	83.65 ± 64.9	66.31 ± 39.2	0.10
SAT (cm^2)	137.40 ± 104.3	101.93 ± 63.4	0.04
SATI (cm^2/m^2)	47.98 ± 38.7	34.70 ± 21.9	0.03
VAT (cm^2)	82.64 ± 65.5	76.32 ± 52.0	0.57
VATI (cm^2/m^2)	28.16 ± 22.3	25.73 ± 16.9	0.51
VAT/SAT ratio	0.78 ± 0.6	1.13 ± 1.4	0.09
IMAT (cm^2)	22.73 ± 31.1	18.38 ± 23.6	0.40
IMATI (cm^2/m^2)	7.92 ± 11.4	6.33 ± 7.9	0.38
SMT (cm^2)	112.55 ± 39.1	116.46 ± 34.5	0.57
SMI (cm^2/m^2)	38.31 ± 11.9	38.73 ± 9.0	0.83
Sarcopenia	29 (61.7)	39 (58.2)	0.75
CrF	3 (6.3)	26 (38.8)	<0.001

Continuous variables are reported as median value ± standard deviation.
TAT, total adipose tissue; TATI, total adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SMT, skeletal muscle tissue; SMI, skeletal muscle index; CrF, creeping fat.

in 68 patients. There was no significant difference between the mild-to-moderate disease and severe disease groups ($p = 0.75$).

There was no significant difference regarding the total MaRIA score (continuous variable) among the groups of dichotomized body composition variables [(low SATI vs. high SATI; $p = 0.73$), (low vs. high VATI; $p = 0.61$), (low vs. high VAT/SAT ratio; $p = 0.12$) (without vs. with sarcopenia; $p = 0.30$)]. Patients with CrF had a significantly higher MaRIA score (25.97 ± 11.1) compared to patients without CrF (18.08 ± 12.0) $p \leq 0.001$. These results are displayed in the Supplementary Table 2.

3.3. Body composition predictors based on dichotomous traits

In the univariate analysis and multivariate analysis CrF was significantly associated with severe disease (OR: 10.72, 95% CI 3.01–38.14; $p \leq 0.001$) and (OR: 11.50, 95% CI 3.13–42.17; $p \leq 0.001$) respectively. In the multivariate analysis, a BMI ≥ 25 (kg/m^2) was protective against severe disease activity (OR: 0.34, 95%CI 0.12–0.95; $p = 0.04$). Male gender, age at diagnosis ≥40 years, high SATI, high VATI, high VAT/SAT, or sarcopenia were not significantly associated with severe disease. These results are displayed in Table 3.

4. Discussion

In the present study, body composition parameters and CrF as predictors of severe CD based on the MaRIA score were retrospectively analyzed. Depending on their MaRIA score, patients were divided into two groups: mild-to-moderate disease (MaRIA <11, $n = 50$) and severe disease (MaRIA ≥11, $n = 64$). The results presented above revealed a significant association between CrF and severe disease (OR: 11.50, 95% CI 3.13–42.17; $p \leq 0.001$).

Labarthe et al. found that sarcopenia was more common in active compared to inactive CD (OR 2.07, 95%CI 1.02–4.27; $p = 0.046$) [18]. In this study, an active CD was defined according to the presence of clinical symptoms (assessed by Harvey-Bradshaw score) and radiological involvement assessed by MRE, including digestive parietal thickening >9 mm with enhancement, stricturing, or penetrating complications. In our population, sarcopenia was not associated with severe disease (OR. 1.3, 95% CI 0.53–2.40; $p = 0.75$). The reason for this is not apparent since MaRIA is considered the most sensitive and specific MRI method for assessing CD activity (85% and 79%, respectively). Furthermore, the SMI cutoff values to define sarcopenia were different in our study since we used the threshold described by Martin et al., in which the BMI (over or under 25 kg/m^2) in men is taken into account [24]. Prospective studies using MaRIA to evaluate CD activity and SMI cutoff for sarcopenia adjusted for sex and BMI should address this discrepancy. It has been reported that glucocorticoids induce muscle atrophy [26]. In our study, the current treatment with corticosteroids tended to be more common in the severe disease group than in the mild-to-moderate disease group ($p = 0.08$). This higher use of corticosteroids was not reflected in an increased occurrence of sarcopenia. Since information on current drug therapy was not available for all patients, we cannot exclude the effect of the current treatment in our results.

CD is a progressive inflammatory disorder that can lead to stricturing or penetrating complication [20]. MRE can accurately assess CD complications, quantify CD activity, and differentiate between fat compartments (VAT and SAT) [2,15,20]. In our study, 60 patients (52.6%) exhibited complicated disease behavior (B2 or B3). Consistently, most of these patients were classified in the severe disease group according to MaRIA ($p \leq 0.001$). Our results showed that the qualitative assessment of CrF was significantly associated with severe disease. These findings agree with previous results by Althoff et al., who recognized that CrF assessed by MRI was independently associated with a complicated course of CD (OR 3.5, $p \leq 0.5$) [7]. In this study, a complicated CD course was defined by the presence of stricturing or penetrating complications, the need for endoscopic dilatation, or abdominal surgery.

CrF is defined as an expansion of mesenteric adipose tissue. Mesenteric adipocytes have been identified as an important source of local production of CRP and pro-inflammatory cytokines [2,27]. Consistent with this biological observation, in our study, the severe disease group exhibited higher serum CRP levels compared to mild-to-moderate disease. This difference was statistically significant ($p \leq 0.001$). Our results highlight CRP values as a biological disease activity marker in CD patients, as previously described in the literature [2,28]. The MaRIA score does not include mesenteric fat alterations and CrF. In our opinion, insufficient attention has been given to the assessment of CrF in the studies of body composition analysis in CD patients. As stated by Suau et al., this can prevent assessing their potential in predicting response to

Table 3
Univariate and multivariate analysis of risk factors (dichotomous traits) for severe disease (MaRIA ≥11), ($n = 114$).

Category	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-value
Sex, (male)	1.05	0.50–1.05	0.90			
Age ≥ 40 years	1.05	0.40–2.74	0.92			
BMI <18.5 (kg/m^2)	0.95	0.36–2.50	0.91			
BMI 25 ≥ (kg/m^2)	0.93	0.16–0.97	0.04	0.34	0.12–0.95	0.04
High SATI	0.76	0.36–1.61	0.48			
High VATI	0.92	0.36–2.35	0.87			
High VAT/SAT	1.65	0.74–3.65	0.22			
Sarcopenia	1.13	0.53–2.40	0.75			
Positive CrF	10.72	3.01–38.14	<0.001	11.50	3.13–42.17	<0.001

BMI, body mass index; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAT/SAT, visceral-to-subcutaneous fat ratio; CrF, creeping fat.

drug therapy or monitoring CD course [29]. Rimola et al. found that the presence of CrF was a negative predictor of long-term healing of inflammatory lesions in CD patients receiving tumor necrosis alpha (TNF-α) [27]. In this study, the severe inflammatory lesions were assessed by MaRIA score. Our work provides support for further quantitative assessment of CrF in MRI as marker of severe CD.

Xiong et al. found that CD patients with longer disease duration tend to have lower contents of SAT and VAT as a result of disease consumption [30]. In our study, the initial analysis showed that SATI was significantly higher in the mild-to-moderate disease group compared to the severe disease group ($p = 0.03$). There was no significant difference in disease duration between both groups ($p = 0.14$). In the univariate analysis, high SATI was not significantly associated with severe disease (OR: 0.76, 95%IC 0.36–1.61; $p = 0.48$). It is well known that in obesity, a significant expansion of the SAT and VAT occurs [31]. In our study, BMI $\geq$ 25 (kg/m^2) was a protective factor against severe disease (OR: 0.34, 95%CI 0.12–0.95; $p = 0.04$). These findings are in line with Jain et al., who reported that obesity and overweight in children with newly diagnosed IBD did not have worsened disease activity one year after diagnosis compared to normal-weight children [32]. The observation that obese IBD patients have an increased risk of infectious post-operative complications when compared to non-obese patients may also be explained by the fact that obesity is a contributing factor to comorbidities such as type 2 diabetes and cardiovascular disease [8,33]. The potential effect of comorbidities in CD activity is beyond the scope of our study.

In our study, VATI was not associated with severe disease activity. Labarthe et al. previously reported no significant difference in VATI among CD between patients with active and inactive CD (OR 3.91, 95% IC -3.60–11.9) [18]. Several authors have previously identified that VAT or SAT alone provides limited information regarding the relative distribution of body fat when compared to the VAT/SAT ratio [34]. Bryant et al. found that VAT/SAT ratio was associated with stricturing complications (OR, 1.7, $p = 0.01$) [35]. Our results showed a trend between high VAT/SAT and complicated disease without a statistically significant difference (OR 1.65, 95% CI 0.74–3.65; $p = 0.22$). We suggest, in agreement with the findings by Xiong et al., that differences at the L3 and L5 levels, should be considered when analyzing CD patients, particularly by assessing adipose tissue changes [30]. Besides, changes in adipose tissue, such as a reduction in VAT, can occur after abdominal surgery [36]. In our opinion, for further prospective studies of body composition analysis, in CD patients, the role of surgery beyond mortality and morbidity should be considered.

5. Limitations

A limitation of our study is the monocentric setting. Due to the retrospective design, the anthropometric measurements were obtained from the clinical records. Besides, the information on the current therapy was only available for some patients. Selection biases were contraindications for MRE and perforating complications, which required CT in the emergency setting. A further limitation of our study is the use of non-standardized cut-off values for SATI, VATI, and VAT/SAT ratio for the European population. Due to the small sample size, our analysis did not exclude CD patients in remission among those classified with mild-to-moderate disease activity depending on MaRIA score. The evaluation of the body composition and MaRIA score over time is beyond the scope of this study. The follow-up time for each scan of the patients was not standardized and, therefore, not considered for the analysis.

6. Conclusion

CrF is significantly associated with CD activity.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mri.2023.01.005.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Body Composition Predictors of Complicated Crohn's Disease

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Keywords
Crohn's disease · Fistula · Subcutaneous adipose tissue · Visceral adipose tissue · Sarcopenia

Abstract
Background: High visceral adipose tissue (VAT) and creeping fat (CrF) in Crohn's disease (CD) have been widely recognized. The VAT to subcutaneous adipose tissue (SAT) ratio and sarcopenia have been associated with CD complications. Studies regarding the influence of body composition predictors on CD complications assessed with magnetic resonance enterography (MRE) are scarce. ***Aim:*** The aim of this study was to assess body composition parameters and CrF in opportunistic MRE as predictors of complicated CD. ***Methods:*** This was a retrospective study of 114 patients with inflammatory (n = 54) and complicated (n = 60) CD. The semi-automated assessment of body composition and the qualitative evaluation of CrF were performed. ***Results:*** Body composition parameters did not differ between both groups regarding the body mass index (p = 0.50), total adipose tissue index (TATI) (p = 0.14), subcutaneous adipose tissue index (SATI) (p = 0.17), visceral adipose tissue index (VATI) (p = 0.33), VAT/SAT ratio (p = 0.77), intramuscular adipose tissue (p = 0.64), skeletal muscle index (p = 0.22), and sarcopenia (p = 0.50). 47 strictures, 18 fistulae, and seven abscesses were identified. Fistulae were more likely to occur in patients with CrF (odds ratio [OR] 5.07, 95% confidence interval [CI] 1.76–14.56; p=<0.001) and high VAT/SAT ratio (OR 3.82, 95% CI 1.34–10.85; p = 0.01). ***Conclusion:*** Body composition measurements in CD patients displayed no statistically significant difference between the groups of inflammatory and complicated disease. Nonetheless, CD patients stratified in the group of high VAT/SAT ratio and the presence of CrF should be recognized as risk groups for the occurrence of fistulae.

Introduction

Crohn's disease (CD) is a progressive disorder characterized by recurring inflammation in the gastrointestinal tract [1]. CD behavior is dynamic over time and progression is shaped by the complications [2–4]. CD complications, including stricture, fistula, and abscess are significant events in diseases' course, leading to higher morbidity rates and impaired quality of life, and higher social and economic burden on healthcare systems [5–7].

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Hypertrophy of visceral adipose tissue (VAT) and creeping fat (CrF) in CD patients have been widely recognized [8]. CrF is defined as an expansion of adipose tissue around the inflamed and fibrotic intestine [9]. Hypertrophic VAT releases higher levels of interleukins, leading to increased inflammatory response, promoting damage to the mucosa, and potentially increasing the risk of developing complications [8]. Erhayiem et al. [8], in 2011, recognized a high VAT to subcutaneous adipose tissue (SAT) ratio as a potential risk factor for stricturing and fistulizing complications in CD. Accordingly, Bryant et al. [10], in 2018, suggested the importance of the VAT/SAT ratio as a potential biomarker rather than body mass index (BMI) for stricturing complications in CD.

CD has been traditionally associated with malnutrition and lower body mass index (BMI) [11]. Both are key drivers of low skeletal muscle tissue (SMT) and the consequential loss of function, a condition known as sarcopenia [11, 12]. Grillot et al. [13], in 2020, identified that sarcopenia in CD patients negatively impacts the length of hospital stay and surgical outcomes. Zhou et al. [14], in 2021, reported an association between low SMT and complicated CD.

In CD patients magnetic resonance enterography (MRE) is an essential pillar for diagnosis, assessment of disease severity, and complications (outside the acute setting) [15]. Its advantages included the avoidance of radiation exposure and good diagnostic accuracy [16]. So far, the quantification of body composition parameters in CD has been mainly performed on computer tomography (CT) scans [4, 17–22]. Studies regarding the influence of body composition predictors on CD complications assessed with MRE are scarce. This study aimed at retrospectively assessing body composition parameters and CrF on opportunistic MRE scans as predictors of complicated CD.

Patients and Methods

Setting and Participants

Patients with diagnosed CD who underwent a magnetic resonance imaging (MRI) scan in the University Clinic for Radiology and Nuclear Medicine (University Hospital Magdeburg) between June 2010 and April 2020 were retrospectively assessed. MRE scans were performed to evaluate disease extension, discard complications, or evaluate therapy response. The inclusion criteria were: (1) first MRE chronologically available and (2) anthropometric data in the clinical records. The exclusion criteria were: (1) MRI of the pelvis and (2) strong MRI artifacts. 437 MRI scans were identified, of which 184 were the first MRI scans. 70 MRI scans were excluded due to examination of the pelvic region or imaging artifacts. The final population was composed of 114 MRE scans (CD patients). A flowchart of patient selection is depicted in Figure 1.

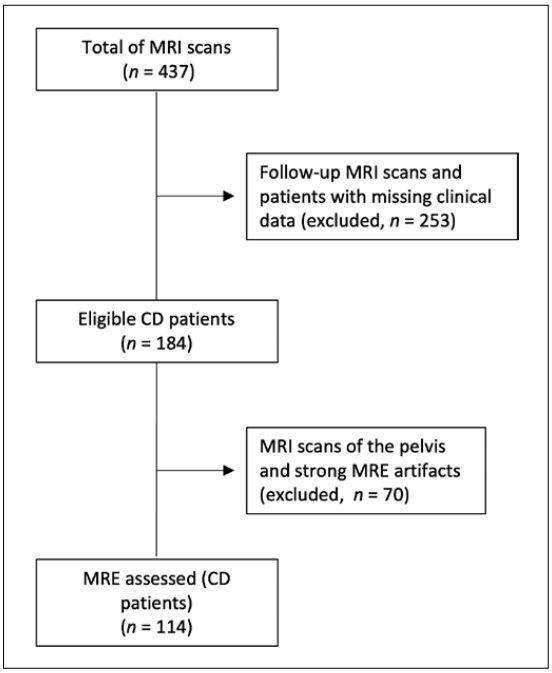

Fig. 1. Flowchart of patient selection. CD, Crohn's disease; MRI, magnetic resonance imaging; MRE, magnetic resonance enterography.

Data Sources and Baseline Characteristics

A search of MRI scans of CD patients was conducted with the picture-archiving and communication system viewing station (INFINITT Healthcare, Seoul, South Korea). Clinical data of the identified patients were extracted from medical records using the internal database (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Germany). Clinical data comprised the gender, age at the baseline and at onset, height, and weight, current CD drug therapy, smoking status, and C-reactive protein (CRP) levels. The age at onset was documented based on the Montreal classification as follows: A1 (less than 16 years), A2 (between 17 and 40 years), or A3 (over 40 years) [3].

MRE Technique

Each MRE scan was performed on a 1.5 T MRI scanner (Intera, Philips Medical Systems, Best, The Netherlands). Optimal small bowel imaging depends on adequate bowel dilatation. The MRE protocol included preparation with fasting overnight. On the day of examination, bowel dilatation was reached through oral administration of 1200 mL of 2.5% sorbitol in small aliquots over 4 h before the examination [18]. Inhibition of intestinal motility was in-

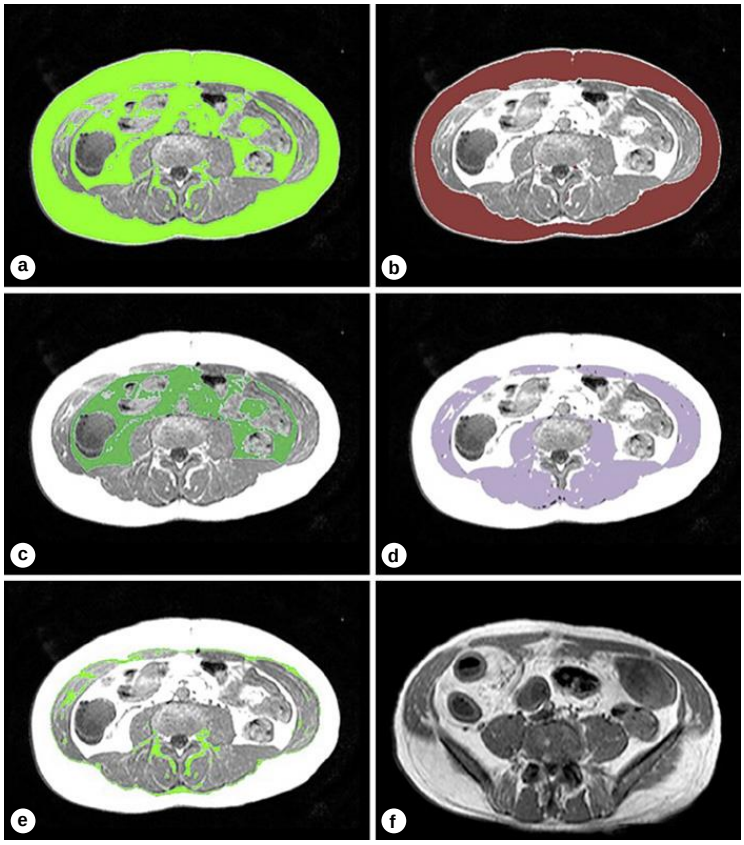

Fig. 2. Segmentation of body composition based on cross-sectional area (CSA) measurements at the L3 inferior endplate level in MRE (**a**–**e**). **a** Total adipose tissue (TAT). **b** Subcutaneous adipose tissue (SAT). **c** Visceral adipose tissue (VAT). **d** Skeletal muscle tissue (SMT). **e** Intramuscular adipose tissue (IMAT). **f** Creeping fat (CrF), T1-weighted MRE image shows fatty deposition along the mesenteric border of inflamed bowel segment.

duced by applying intravenously 20 mg/mL of N-butylscopolamine (Buscopan, Boehringer Ingelheim, Germany). A gadolinium-based MRI contrast agent (Gadovist, Bayer Vital, Leverkusen, Germany) was administrated as an intravenous bolus injection at approximately 0.1 mL/kg. The MRE sequences are displayed in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529426).

Assessment of Complications and Creeping Fat

Each MRE scan was reviewed in tandem by two physicians to get agreement about the measurements: one senior radiology resident with 4 years of experience in the field of abdominal-pelvic MRI and a senior staff radiologist with more than 15 years of experience in the same field. For each scan, the following aspects were evaluated: (1) visible small bowel stricture, defined as a small bowel lumen <10 mm with or without prestenotic dilatation considering a prestenotic lumen >30 mm dilatation, (2) visible fistula, defined as an abnormal communication between the small bowel, and other organs, (3) visible abscess, defined as an encapsulated collection containing pus and/or gas, and (4) the presence or absence of CrF, defined as fatty deposition along the mesenteric border of inflamed bowel segment [18, 21, 23]. Depending on the MRE findings, patients were divided into inflammatory and complicated disease. Complicated disease was defined as the presence of stricture, fistula, or abscess [3, 4, 6].

Assessment of Body Composition

Body composition measurements were performed on MRE scans using the semiautomated segmentation tool AsanJ-Morphometry software (Asan Image Metrics, Seoul, Korea) [24]. The software was operated by a senior radiology resident with 4 years of experience in the field of abdominal-pelvic MRI. The cross-sectional area (CSA) measurements were evaluated at the L3 inferior endplate level. The body composition measurement at this level has often been used as a reference in clinical routine and has been the reference location for analyzing body composition [25]. It included the estimation of total adipose tissue (TAT), SAT, VAT, SMT, and intramuscular adipose tissue (IMAT) in square centimeters (cm^2) based on the pixel count (Fig. 2). Muscle and adipose tissues were separated using thresholds for the signal intensity (SI) on precontract T1-weighted MRE scans with a value above 350 SI and lower 750 SI for adipose tissue and above 100 SI and lower 350 SI for muscle.

Table 1. Baseline characteristics of all CD patients (n = 114)

	All CD patients, (n = 114), n (%)	Inflammatory disease (n = 54), n (%)	Complicated disease, (n = 60), n (%)	p value
Male	60 (52.6)	30 (55.6)	30 (50.0)	0.55
Age at baseline (years), median, [IQR]	35.50 [27.0–46.3]	38.50 [26.8–47.3]	33.00 [27.0–45.0]	0.91
Age at diagnosis (years), median, [IQR]	26.00 [17.0–36.0]	28.00 [17.0–35.3]	25.50 [17.0–36.8]	0.84
Age of onset				
A1	24 (21.1)	11 (20.4)	13 (21.7)	0.87
A2	69 (60.5)	35 (64.8)	34 (56.7)	0.37
A3	21 (18.4)	8 (14.8)	13 (21.7)	0.35
Current drug therapy[a]				
Corticosteroids	36 (31.6)	19 (35.9)	17 (28.3)	0.27
Biological therapy	22 (19.3)	11 (20.4)	11 (18.3)	0.63
Immunomodulator	25 (21.9)	14 (25.9)	11 (18.3)	0.22
5-aminosalicylic acid	14 (12.3)	5 (9.2)	9 (15.0)	0.41
Current smoker	13 (11.4)	6 (11.1)	7 (11.7)	0.93
CRP (>5 ng/mL)	88 (77.2)	40 (74.1)	48 (80.0)	0.45
BMI (kg/m^2), median, [IQR]	21.94 [19.4–24.9]	21.32 [18.8–35.3]	22.21 [19.5–25.2]	0.50
BMI <18.5 kg/m^2	20 (17.5)	11 (20.4)	9 (15.0)	0.45
BMI 18.5–24.9 kg/m^2	68 (59.6)	32 (59.3)	36 (60.0)	0.94
BMI >25 kg/m^2	26 (22.8)	11 (20.4)	15 (25.0)	0.56

Continuous variables are reported as median and interquartile range (IQR). CD, Crohn's disease; CRP, C-reactive, protein; BMI, body mass index. [a] Current therapy information was available for 99 patients only.

Body Composition Groups

BMI was calculated by using the formula [weight (kg)/height squared (m^2)] [26]. BMI categories were subdivided as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), and overweight/obese (≥25.0 kg/m^2) [27]. Sarcopenia was measured in terms of skeletal muscle index (SMI) [12]. The SMI was calculated by dividing the SMT (cm^2) by height squared (m^2) [26]. The SMI cutoff values to define sarcopenia for men were 43 (cm^2/m^2) under a BMI of 25 (kg/m^2) and 53 (cm^2/m^2) over a BMI of 25 kg/m^2, respectively, and 41 (cm^2/m^2) for women [26, 28]. To calculate TATI, SATI, and VATI, TAT (cm^2), SAT (cm^2), and VAT (cm^2) were divided by the height squared (m^2), respectively. The sex-specific cutoff values for the classification of SATI (low/normal vs. high SATI) were 40 (cm^2/m^2) for men and 30 (cm^2/m^2) for women; for VATI (low/normal vs. high VATI) 44.0 (cm^2/m^2) for men and 35 (cm^2/m^2) for women; and for VAT/SAT ratio (low/normal vs. high VAT/SAT ratio) 1.08 for men and 0.86 for women [29, 30].

Statistical Analysis

Continuous variables, including body composition parameters, are shown as mean (M) and standard deviation (SD) or median and interquartile range (IQR). The Kolmogorov-Smirnov test was used to assess the normality of the continuous variables. Continuous variables were compared between the groups of inflammatory and complicated CD using the student's t test. The Mann-Whitney U test was used to assess continuous, not normally distributed variables. Categorical variables, including CrF, were compared using the χ^2 test or Fisher's exact test, as appropriate. A binary logistic regression model for body composition groups based on sex-specific values was performed to evaluate the factors associated with stricture, fistula, and abscess. Odds ratio (OR) is presented together with 95% confidence interval (CI). A two-tailed p value ≤0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) was used as analytic software.

Results

Patient Characteristics

The baseline characteristics of our population (n = 114) are shown in Table 1. The median age at baseline was 35.50 years (IQR, 27.0–46.3). The majority of patients were male (n = 60, 52.6%), and the median BMI was 21.94 (kg/m^2) (IQR, 19.4–24.9). We identified 54 patients with inflammatory and 60 with complicated CD. The groups of inflammatory and complicated disease were well-matched for gender, age at the baseline, age of onset, current drug therapy, current smoking status, BMI categories, and CRP levels (>5 ng/mL).

Comparison of the Body Composition Parameters in the Inflammatory and Complicated Disease

Body composition parameters in the groups of inflammatory and complicated disease are listed in Table 2.

Table 2. Body composition parameters in the groups of inflammatory and complicated CD ($n = 114$)

Parameter	Inflammatory disease, total ($n = 54$)	Complicated disease total ($n = 60$)	p value
TAT (cm^2), median [IQR]	159.45 [110.2–250.6]	196.45 [126.6–287.5]	0.17
TATI (cm^2/m^2), median [IQR]	57.23 [36.5–85.8]	69.23 [42.9–98.2]	0.14
SAT (cm^2), median [IQR]	92.75 [46.2–139.4]	109.40 [63.0–184.0]	0.22
SATI (cm^2/m^2), median [IQR]	30.75 [14.4–50.7]	36.20 [20.0–61.1]	0.17
VAT (cm^2), median [IQR]	59.55 [38.0–95.5]	69.45 [45.9–96.6]	0.37
VATI (cm^2/m^2), median [IQR]	21.44 [13.3–34.5]	26.87 [15.2–35.1]	0.33
VAT/SAT ratio, median [IQR]	0.70 [0.4–1.1]	0.70 [0.4–1.2]	0.77
IMAT (cm^2), median [IQR]	3.85 [1.9–8.3]	3.95 [2.4–4.0]	0.64
SMT (cm^2), M ± SD	111.14±36.57	117.99±36.35	0.32
SMI (cm^2/m^2), M ± SD	37.30±10.39	39.67±10.18	0.22

Continuous variables are reported as mean (M) ± standard deviation (SD), or median and interquartile range (IQR). TAT, total adipose tissue; TATI, total adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; IMAT, intramuscular adipose tissue; SMT, skeletal muscle tissue; SMI, skeletal muscle index; M, mean; SD, standard deviation.

Table 3. Body composition groups based on sex-specific values, creeping fat, and occurrence of complicated disease ($n = 114$)

Groups	Patients with inflammatory disease, total ($n = 54$), n (%)	Patients with Complicated disease total ($n = 60$), n (%)	p value
Low/normal SATI	31 (27.2)	28 (24.6)	0.25
High SATI	23 (20.2)	32 (28.1)	
Low/normal VATI	44 (38.6)	48 (42.1)	0.84
High VATI	10 (8.8)	12 (10.5)	
Low/normal VAT/SAT ratio	37 (32.5)	38 (33.3)	0.56
High VAT/SAT ratio	17(14.9)	22 (19.3)	
Non-sarcopenic	20 (17.5)	26 (22.8)	0.50
Sarcopenic	34 (29.8)	34 (29.8)	
CrF absent	44 (38.5)	41 (35.9)	0.11
CrF present	10 (8.7)	19 (16.6)	

SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAT/SAT ratio, visceral-to-subcutaneous fat ratio; CrF, creeping fat.

There was no significant difference between both groups regarding TAT ($p = 0.17$), TATI ($p = 0.14$), SAT ($p = 0.22$), SATI ($p = 0.17$), VAT ($p = 0.37$), VATI ($p = 0.33$), VAT/SAT ratio ($p = 0.77$), IMAT ($p = 0.64$), SMT ($p = 0.32$), and SMI ($p = 0.22$).

Comparison of Body Composition Groups Based on Sex-Specific Cutoff Values of Values, CrF, and Complications

Patients were classified into body composition groups based on sex-specific cutoff values. There were no significant differences in the occurrence of complicated disease (including all stricturing and penetrating complications) in the groups of SATI (low/normal vs. high SATI) ($p = 0.25$), VATI (low/normal vs. high VATI) ($p = 0.84$), and VAT/SAT ratio (low/normal vs. high VAT/SAT ratio) ($p = 0.56$). Sarcopenia was identified in 68 patients (59.6%) and did not differ in the groups of inflammatory and complicated disease ($p = 0.50$). CrF was identified in 29 patients. There was no significant difference in the occurrence of complicated disease if CrF was present ($p = 0.11$). Table 3 summarizes these findings.

A total of 47 strictures, seven abscesses, and 18 fistulae were identified among the patients with complicated dis-

Table 4. Body composition groups, creeping fat, and occurrence of fistulae (n = 114)

Groups	Patients without fistula, total (n = 96), n (%)	Patients with fistula, total (n = 18), n (%)	p value
Low/normal SATI	48 (50)	11 (61.1)	0.39
High SATI	48 (50)	7 (38.9)	
Low/normal VATI	77 (80.2)	15 (83.3)	1.00
High VATI	19 (19.8)	3 (16.7)	
Low/normal VAT/SAT ratio	68 (70.8)	7 (38.9)	0.01
High VAT/SAT ratio	28 (29.2)	11 (61.1)	
Non-sarcopenic	40 (41.7)	6 (33.3)	0.51
Sarcopenic	56 (58.3)	12 (66.7)	
CrF absent	77 (80.2)	8 (44.4)	<0.001
CrF present	19 (19.8)	10 (55.6)	

SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAT/SAT ratio, visceral-to-subcutaneous fat ratio; CrF, creeping fat.

Table 5. OR and 95% CI for the occurrence of fistula (n = 114)

Groups	OR	95% CI	p value
High SATI versus low/normal SATI	0.64	0.28–1.78	0.86
High VATI versus low/normal VATI	0.81	0.23–3.09	0.76
High VAT/SAT versus low/normal VAT/SAT	3.82	1.34–10.85	0.01
Sarcopenic versus non-sarcopenic	1.43	0.50–4.13	0.51
CrF present versus CrF absent	5.07	1.76–14.56	<0.001

SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAT/SAT, visceral-to-subcutaneous fat ratio; CrF, creeping fat; OR, odds ratio; CI, confidence intervals.

Table 6. OR and 95% CI for the occurrence of stricture (n = 114)

Groups	OR	95% CI	p value
High SATI versus low/normal SATI	1.21	0.57–2.56	0.50
High VATI versus low/normal VATI	0.78	0.30–2.03	0.61
High VAT/SAT versus low/normal VAT/SAT	0.99	0.45–2.17	0.97
Sarcopenic versus non-sarcopenic	0.63	0-30–1.36	0.24
CrF present versus CrF absent	1.77	0.76–4.15	0.19

SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAT/SAT, visceral-to-subcutaneous fat ratio; CrF, creeping fat.

ease. The occurrence of each complication was also assessed in each group of body composition. Only the groups with a high VAT/SAT ratio and CrF demonstrated a significant difference in the occurrence of fistulae (p = 0.01 and p = <0.001, respectively) (Table 4). None of the groups demonstrated a significant difference in the occurrence of abscesses (online suppl. Table 2a) or strictures (online suppl. Table 2b). The occurrence of CrF tended to be more common in patients with stricturing complications when compared to patients without stricturing complications (p = 0.18) (online suppl. Table 2b).

The association of the body composition groups, CrF, and CD complications was further explored by estimating the OR for the occurrence of fistulae (Table 5), strictures (Table 6), and abscesses (online suppl. Table 3). CrF (OR 5.07, 95% CI 1.76–14.56; p = <0.001) and high VAT/SAT ratio (OR: 3.82, 95%, CI 1.34–10.85; p = 0.01) were positively associated with the occurrence of fistulae. Nei-

ther the body composition groups nor CrF demonstrated a significant association for developing stricture or abscess in our population.

Discussion

To our knowledge, this is the first study to comprehensively evaluate the association of body composition parameters using a standardized MRE-based semiautomated tool, CrF, and CD complications. Altered body composition parameters and clinical factors such as the age of onset (<40 years), perianal disease, the initial requirement for steroids, early use of anti-inflammatory agents, and smoking history (prior appendectomy) have been suggested as risk factors of complicated CD [8, 10, 11, 14, 31, 32]. Since the duration of CD may last more than 50 years; identifying risk factors for complicated disease over such a long time frame remains extremely difficult [2]. Our data suggest that the occurrence of fistulae is more common in CD patients with a high VAT/SAT ratio or in the presence of CrF.

CD has been traditionally associated with malnutrition and lower BMI [13]. However, the prevalence of obesity in CD patients is increasing [33]. According to a recent metanalysis by Jiang et al. [34] in 2022, obese inflammatory bowel disease patients have an increased risk of surgical complications (OR = 1.45, p=<0.001), particularly infectious complications (OR = 1.48, p = 0.003) when compared to nonobese patients (including overweight). The impact of obesity on CD behavior has not always been consistent throughout the literature [35]. In our study, BMI did not differ between the groups of inflammatory and complicated disease (p = 0.50). 22.8% of our patients had a BMI ≥25 kg/m^2. Due to the small sample size, patients presenting a BMI higher than 25 kg/m^2 were not further categorized. Nevertheless, the group of patients with overweight or obesity did not show an increased occurrence of complicated disease (p = 0.56). These results are in line with other authors suggesting that BMI alone is not related to disease behavior [10, 33].

Several authors have mentioned that using visceral adiposity as a measure of obesity has more consistently shown an increase in CD complications than using BMI as a marker of obesity [8, 33, 35, 36]. Thiberge et al. [37], in 2018, reported that lower SATI (p = 0.009) and VATI (p = < 0.001) were inversely correlated with adverse postoperative outcomes in CD patients. In contrast, in our study, TATI, SATI, and VATI did not differ between the groups of complicated and inflammatory disease (p = 0.14, p = 0.17, and p = 0.33, respectively). Our results are in line with Labarthe et al. [15], showing no significant difference in VATI (p = 0.34) among CD patients with active compared to inactive disease. The further categorization of our population based on sex-specific cutoff values of SATI (low/normal vs. high SATI) and (low/normal vs. high VATI) did not predict the occurrence of any specific complication (fistulae, abscesses, or strictures). Our data suggest that VAT, VATI, SAT, and SATI alone are inadequate to predict CD complications.

Altered body composition with the development of changed mesenteric adipose tissue is characteristics of CD [35]. The production of tumor necrosis factor α as part of an increased inflammatory response in adipose tissue has been well-documented [38]. According to Kaess et al. [39], VAT or SAT alone provides limited information regarding the relative distribution of body fat when compared to the VAT/SAT ratio. Conelly et al. [33] suggested that the VAT/SAT ratio was also a more reliable predictor of postoperative morbidity in CD patients undergoing an ileocecectomy than BMI (p = 0.03). The role of VAT/SAT in CD complications was further explored by Erhayiem et al. [8], who found that the mean VAT/SAT ratio was significantly higher in CD patients with stricturing or fistulizing complications compared to those with uncomplicated disease (p = 0.001). In their study, 29 patients with complicated disease were evaluated and the body composition measurements were performed at the L4 level on CT scans, which is not a standard reference location for analyzing body composition parameters [8, 15, 25]. In contrast, our study included a slightly higher amount of patients with complicated disease (n = 54), and among penetrating complications alongside fistulae, abscesses were included. The reported high VAT/SAT ratio by Erhayiem et al. was not specific for stricture or fistula. Our data suggest that the use of sex-specific cutoff values for VAT/SAT ratio can be crucial regarding the identification of patients with fistulizing complications (OR: 3.82, 95%, CI 1.34–10.85; p = 0.01). Unlike Erhayiem et al., the segmentation of the images in our study was performed using a semiautomated tool on MRE scans at the L3 level, which is a more reproducible tool. In our population, VAT/SAT alone was not associated with a higher recurrence of abscesses (OR: 1.48, 95%, CI 3.14–6.97; p = 0.36). The power to detect an association was very limited due to the small number of patients with abscesses (n = 7). The differences in body composition parameters within penetrating disease behavior (fistulae and abscesses) remain a topic for further research.

Whether a high VAT/SAT ratio is associated with fistulizing complications is still under debate. In 2015, Büning et al. [36] showed that CD patients with stricturing and fistulizing complications had a high VAT/total fat mass (FM) ratio. In this particular study, VAT was measured with MRI; however, the total FM, with air-displacement plethysmography. Furthermore, only women in clinical remission were included and the administrations of systemic corticosteroid treatment (3 months before the study), severe weight loss (10% of body weight within 6 months before the study), as well as the presence of an ileostomy or colostomy were exclusion criteria. Our population included all CD patients regardless of disease activity, current medication, or prior surgeries, which is more representative of the heterogeneity of the CD population undergoing MRE in clinical routine. Furthermore, the use of air-displacement plethysmography is not a commonly established diagnostic procedure in CD monitoring, which may limit its clinical utility [36].

Bryant et al. [10] suggested that VAT/SAT ratio was associated with stricturing disease behavior (log OR: 1.7; CI, 0.32–3; $p = 0.01$) but not with fistulizing disease. In their study, CD patients between 18 and 50 years were included and VAT/SAT assessment was based on dual-energy X-ray absorptiometry. Furthermore, the classification of complications at baseline was based on clinical data. In contrast, in our study, the definitions of CD-related complications were performed based on the revaluation of the MRE scans, which is a more accurate method to define complicated disease. In our study, a high VAT/SAT was not associated with a higher occurrence of stricturing complications (OR: 0.99, 95%, CI 0.45–2.17; $p = 0.97$). The reason for this is not apparent. Considering that dual-energy X-ray absorptiometry assessment for patients with large VAT values has a poor correlation with MRI and that the gold standard for measuring and analyzing visceral fat comprises MRI and CT our results could not confirm the previous findings of Bryant et al. [10, 40].

CrF has been traditionally associated with small intestinal fibrosis and is characterized by finger-like projections of mesenteric adipose tissue around the inflamed bowel [41]. Data from macroscopic findings indicated that the presence of CrF was associated with hyperplasia of muscularis propia, changes in connective tissue, and ultimately the development of stricture [42]. In a study by Li et al. [43], the degree of CrF assessed by CT was associated with intestinal fibrotic strictures in CD patients ($p = 0.018$). Even so, the association between CrF and stricturing complications is biologically plausible. In our study, the occurrence of CrF in patients with stricturing complications when compared to patients without stricturing complications was not significantly different ($p = 0.18$). The reason for this is not apparent. It has been reported that connective tissue changes including CrF are related to local effects of underlying chronic inflammation [42]. In our study, as well as in previous studies, no distinction between inflammatory and fibrotic stenotic changes was made, being presumably the latter stronger related to adipose tissue changes including CrF [44].

Althoff et al. [45] identified that CrF evaluated by MRI was associated with a complicated course of abdominal surgery in CD patients. In our study, CrF tended to be more common in patients with complicated compared to inflammatory disease ($p = 0.11$). In our population, fistulizing complications rather than stricturing complications were more likely to occur in patients with CrF (OR 5.07, 95% CI 1.76–14.56; $p = <0.001$). The observation that CrF was common in patients with fistulae is plausible since CrF has been described as a protective response where mesenteric adipose tissue migrates to sites of gut barrier dysfunction to prevent systemic dissemination of potentially harmful bacterial antigens that have translocated across the barrier from the gut lumen [9]. Furthermore, some bacteria might directly infect endothelial cells and adipocytes, causing them to proliferate, ultimately generating the development of new vessels and CrF of the mesentery [9, 46]. As a result, the walls of fistulae might result from neoangiogenesis or lymphangiogenesis that occurs in the bowel wall [46].

The incidence of sarcopenia in our population was 59.6%. This is higher compared with the previous incidence reported by Thiberge et al. [37] (33.6%) and comparable with the incidence in CD patients reported by Labarthe et al. [15] (50%). In a meta-analysis by Erős et al. [47], in 2020, sarcopenia was identified as an independent predictor for rate of surgery (OR = 1.826; 95% CI 0.913–3.654; $p = 0.089$). In our study, sarcopenia was not associated with the occurrence of complicated disease. Even though both groups were well-matched for current drug therapy, this clinical information was available for only 86.8% of the patients. As it is well known that glucocorticoids induce muscle atrophy, we cannot exclude that these results were influenced by the current CD-related therapies [48].

As described by Labarthe et al. [15] MRI measurements of body composition parameters are feasible and reproducible, particularly with the help of semiautomated methods. MRE has a higher accuracy in detecting CrF and fistula than CT; the avoidance of radiation exposure

is also an advantage [23]. The clinical perspective offered by our data suggests that the MRE-based stratification of CD patients in high VAT/SAT group, as well as the radiological assessment of CrF, should be recognized as a new potential prognostic factor for the occurrence of fistulizing complications. Our results should generate further studies, particularly focusing on the quantitative assessment of CrF in MRE. Ultimately the clinical utility and setting (assessment at diagnosis, monitoring symptomatic or asymptomatic patients, or postoperative follow-up) must be determined in prospective multicentric studies. In agreement with Xiong et al. [49], we consider that differences at the L3 and L5 levels, in addition to the L3 level, should be studied when analyzing body composition parameters in CD patients, particularly by assessing adipose tissue changes. The impact of body composition changes over time on disease behavior also requires further investigation.

Our study has some limitations, CD patients with contraindications for MRE, such as electrically, magnetically, or mechanically activated devices or known adverse reactions to gadolinium contrast media, were not included in our study [21]. In our study, the anthropometric data were obtained from clinical records, which could not be verified. Additionally, the quantification of body composition parameters from MRE scans has not been completely standardized, and there is wide variability concerning protocol optimization. The retrospective methodology of the study did not allow a rigorous evaluation of body composition changes over time or the consideration of the role of surgery and current drug therapies as additional factors to predict complicated disease. CD patients with acute intestinal complications like low intestinal bleeding, perforation, and intestinal obstruction were not included. Besides, in acute settings at our institution, most of the CD patients presenting an abscess undergo a CT scan. The small sample size of patients presenting penetrating complications, particularly abscesses is another limitation of our study.

Conclusions

Body composition measurements in CD patients displayed no statistically significant difference between the groups of inflammatory and complicated disease. Nonetheless, CD patients stratified in the group of high VAT/SAT ratio and the presence of CrF should be recognized as risk groups for the occurrence of fistulae.

Statement of Ethics

This study was conducted according to the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board Ethics Committee (Number: 145/21), Otto-von-Guericke University, Magdeburg, Germany. For this retrospective study, the requirement of informed consent was waived.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

AS and FB conceived and designed the study; FB, OM, MT, and BM contributed to the collection of the clinical data and BM performed the segmentation of the MRE scans. AS and BM evaluated the MRE scans. FB and PR contributed to the manuscript writing. FB and RD contributed to the statistical analysis. MP, JO, and PR contributed to the critical revision of the manuscript. All authors approved the final manuscript for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author (FB).

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Original paper

Diagnostic value of apparent diffusion coefficient of psoas muscles for evaluating complications in patients with Crohn's disease

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Abstract

Aim: To assess the association of the apparent diffusion coefficient (ADC) of the psoas muscles and psoas muscle index (PMI) with the activity and behaviour of Crohn's disease (CD).

Material and methods: This was a retrospective study of 88 CD patients who underwent magnetic resonance enterography. Patients were classified according to the Montreal Classification in uncomplicated (non-stricturing, non-penetrating, B1), and complicated (structuring [B2] and penetrating disease [B3]). At the level of the third lumbar vertebra, the ADC and PMI were estimated. CD activity was analysed using the Magnetic Resonance Index of Activity (MaRIA), and depending on its values patients were categorized as high or low activity. Additionally, the presence of creeping fat (CrF) was used to evaluate activity. ADC and PMI were using Student's *t*-test.

Results: Our study included 47 males and 41 females (mean age of 38.69 ±14.4 years). The ADC in uncomplicated (B1, $n = 45$) and complicated disease (B2 + B3, $n = 43$) were 1.11 ±0.19 and 1.03 ±0.10 (10^{-3}*mm^2/s), respectively, ($p = 0.02$). ADC was significantly lower in patients with stricturing disease than in patients without strictures (1.02 ±0.11 and 1.10 ±0.18 [10^{-3} mm^2/s], respectively, $p = 0.01$). The group with non-penetrating disease showed higher PMI than those with penetrating disease (5.71 ±1.88 vs. 4.42 ±1.55 cm^2/m^2, respectively, $p = 0.10$). There was no significant difference in PMI and ADC between patients with low and high MaRIA or positive and negative CrF.

Conclusions: The ADC of the psoas muscles is significantly lower in CD patients with uncomplicated disease, particularly those with stricturing disease. Therefore, ADC can be considered as an imaging biomarker of myopathic changes in CD patients.

Introduction

Crohn's disease (CD) is a chronic progressive, relapsing, and remitting inflammatory condition affecting the gastrointestinal tract, and in 30% of patients it leads to complications such as strictures, fistula, abscesses, and perianal forms [1]. According to a meta-analysis by Yaron in 2020, CD complications can lead in up to 23.3% of cases to hospitalization, and in 12.4% to further surgical treatment [2]. Despite the increasing development of new medications, medical or surgical hospitalization remains central to all direct healthcare costs, reaching in 2020 approximately 3500 Euro per CD patient per year [3, 4].

Penetrating disease, perianal or foregut involvement, young age at the time of diagnosis (< 40 years), smoking, and early start of corticosteroid therapy have been identified as high-risk features for required surgery (risk ratio (RR) 13.67, 95% confidence interval (CI) 1.88–99.41) and hospitalization (RR = 1.86, 95% CI: 0.03–0.43) [5]. In a recent systemic review by Tang *et al.* in 2023, body composition parameters were shown to predict poor outcomes for CD patients [6]. Sarcopaenia was associated with longer disease duration, more

complex phenotype, and disease activity [6]. Additionally, sarcopaenia was revealed as a risk factor for the requirement of surgical intervention (hazard ratio (HR) = 4.31, 95% CI: 1.36–13.7) and for postoperative complications (HR = 3.84, 95% CI: 1.48–9.974) [6–8].

Sarcopaenia as progressive and generalized degenerative loss of skeletal muscle mass occurs in CD patients primarily due to malnutrition caused by chronic bowel inflammation (IBD). A population-based study by Sharif *et al.* in 2022, including 2085 patients with polymyositis (PM) and dermatomyositis (DM) and 10,193 patients as a control group, demonstrated the incidence of IBD in PM/DM patients to be significantly higher (OR = 1.73, 95% CI: 1.05–2.86) [9]. Its results, such as reported clinical cases of the appearance of ocular or gastrocnemius myositis in CD patients, confirm the hypothesis of a crucial role of low-grade systemic inflammation in the disturbance of skeletal muscle homeostasis leading to sarcopaenia [10–13].

Thus, there is a need for additional methods of assessing the degree of muscle mass loss and the detection of intramuscular disorders like low-grade inflammation, which can significantly expand our diagnostic and prognostic values in patients with Crohn's disease. In recent studies, it was demonstrated that diffusion-weighted imaging quantified by apparent diffusion coefficient can reflect intramuscular microstructure disorders, for example, in the case of tumours or muscle cell lysis in myositis [14, 15]. Furthermore, in 2018, Surov *et al.* showed that ADC can be used as an imaging biomarker of myopathic changes in liver cirrhosis [16].

Aim

Therefore, the aim of this study was to assess the relationship between ADC values of the skeletal musculature and the activity or behaviour of CD as high-risk features.

Material and methods

Our retrospective study was conducted in the University Clinic for Radiology and Nuclear Medicine (University Hospital Magdeburg) and approved by the Institutional Review Board Ethics Committee (Number: 145/21), Otto-von-Guericke University, Magdeburg, Germany. Patients with confirmed CD, who underwent magnetic resonance enterography (MRE) between June 2010 and April 2020 were included. Each MRE was performed on a 1.5 Tesla MR scanner (Intera, Philips Healthcare, Best, Netherlands) in a supine position using a whole-body surface coil system. Our MRE protocol has been previously reported, and the MRI sequences are summarized in Supplementary Table SI [17, 18].

Clinical data were extracted from our internal database (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Germany) and comprised sex, weight,

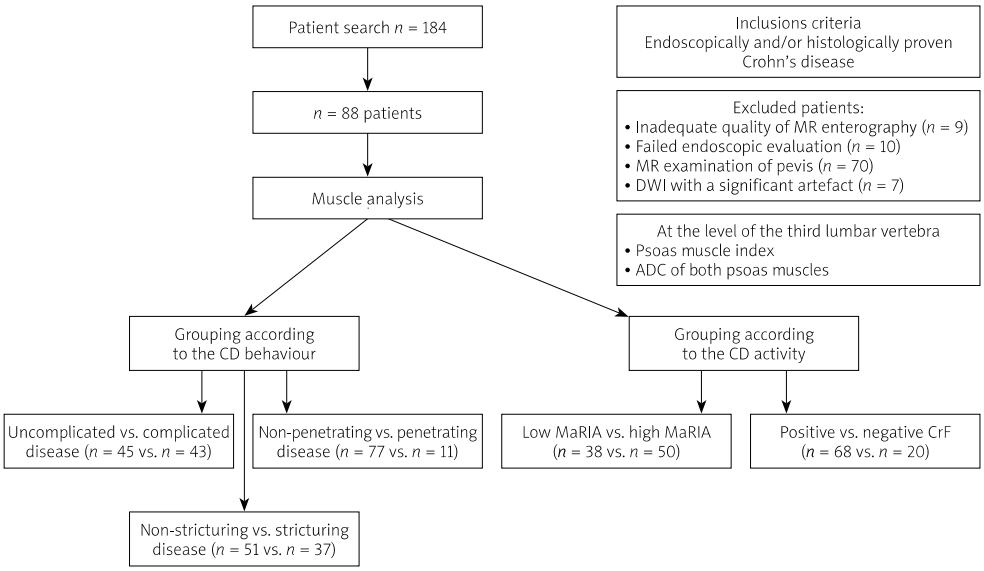

Figure 1. Study design

CD – Crohn's disease, CrF – creeping fat, MaRIA – Magnetic Resonance Index of Activity, DWI – diffusion-weighted imaging, ADC – apparent diffusion coefficient.

height, age, smoking, duration of disease, CRP, complications (stricture, fistula, abscess), medications, and previous abdominal surgery. The study design is depicted in Figure 1, and it included muscle analysis and assessment of CD activity and complications.

Setting and participants

Our inclusion criteria were as follows: (a) endoscopically and/or histologically confirmed CD, (b) complete demographic and clinical data, (c) the first MRE chronologically available, (d) performed DWI without reduced quality.

The exclusion criteria were as follows: (a) incomplete clinical data (b) strong MRE artifacts, and (c) MRI of the pelvic region.

Muscle analysis

We performed our assessment at the level of the third lumbar vertebra. The analysis included measuring the cumulative mean ADC value of both psoas muscles. ADC value was measured by drawing polygonal regions of interest (ROI) along the contours of the psoas muscles in ADC maps, avoiding fat areas and vessels. The ROI placement is demonstrated in Figure 2.

The psoas muscle area was estimated using the special semi-automated tool AsanJ-Morphometry (available at http://datasharing.aim-aicro.com/en/morphometry) also at the same level [19]. The separation of muscle and adipose tissue was performed according to thresholds for the signal intensity on precontrast T1-weighted MRI scans with the values between 350 and 750 signal intensity (SI) for adipose tissue and between 100 and 350 SI for muscle tissue. The psoas muscle index (PMI) was calculated by dividing the psoas muscle areas of both sides by the patient height squared (cm^2/m^2) [20] (Figure 3).

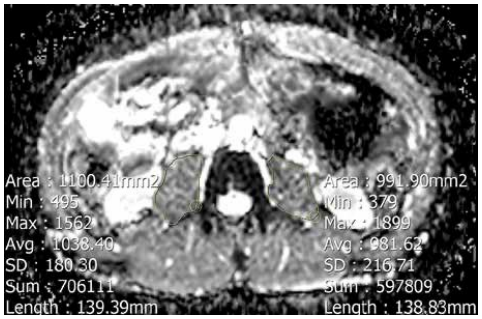

Figure 2. Manual measurement of ADC values of both psoas muscles

Assessment of CD activity

The CD activity we evaluated using the Magnetic Resonance Index of Activity (MaRIA), which was estimated in the segment with the most severe changes according to the formula (1.5 × wall thickness [mm] + 0.02 × relative contrast enhancement [RCE]). RCE was calculated as follows: RCE = (wall signal intensity [WSI] post gadolinium- WSI pre-gadolinium/[WSI pre-gadolinium]) × 100 × (standard deviation [SD] noise pre-gadolinium/SD noise post-gadolinium). SD noise before and after gadolinium administration was performed as the average of 3 SD of the signal intensity measured outside the body. Patients were dichotomized using a cut-off value of MaRIA score into 2 groups: mild-to-moderate disease (MaRIA < 11) and severe disease (MaRIA ≥ 11) [21].

Additionally, each MRE was assessed on the presence of stricture, fistula, abscess, and fatty deposition along an inflamed bowel loop known as creeping fat (CrF) [22, 23]. CD behaviour was categorized according to the Montreal classification into 3 groups: non-stric-

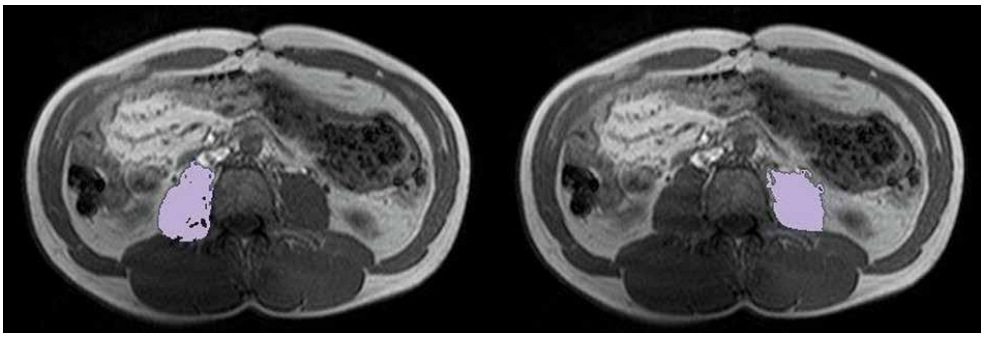

Figure 3. Evaluation of muscle volume of both psoas muscles using the semiautomated segmentation (AsanJ-Morphometry) at the level of the third lumbar vertebra

turing, non-penetrating (B1), stricturing (B2), and penetrating (B3) [24].

Statistical analysis

Continuous variables were expressed as mean (M) and standard deviation (SD). Categorical variables were demonstrated in percentages. Continuous variables were compared between groups using Student's *t*-test. The intraclass correlation coefficient (ICC) of a subset of 30 patients was calculated for each pair of ADC, PMI, and MaRIA values to determine the intra- and interobserver agreement. Also, for CrF as a categorical variable Cohen's κ was used test to evaluate intra- and interobserver agreement. Values of 0.61–0.80 were interpreted as substantial and 0.81–1.00 as excellent agreement. A *p*-value of 0.05 was considered statistically significant. We performed analyses using a statistical software package (SPSS Statistics for Windows, version 27.0, IBM Corp., Armonk, NY, USA).

Table I. Baseline characteristics (n = 88)

Parameter	*N* (%) or mean ± SD
Female	41 (46.6)
Male	47 (53.4)
Age at baseline [years]	38.69 ±14.4
Age at diagnosis [years]:	
A1 < below 16	17 (19.3)
A2 17–40	51 (61.4)
A3 > 40	17 (19.3)
Behaviour:	
B1 non-stricturing, non	45 (51.1)
Complicated disease (B2 + B3):	43 (48.9)
Stricture:	37 (42.0)
Ileal	20 (22.7)
Colonic	6 (6.8)
Ileocolonic	11 (12.5)
Fistula	9 (10.2)
Abscess	5 (5.7)
Previous abdominal surgery	35 (39.8)
Current drug therapy*:	51 (58.8)
Corticosteroids	51 (28.4)
Biological therapy	15 (17.0)
Immunomodulator	19 (21.6)
5-aminosalicylic acid	10 (11.4)
Current smoker	10 (11.4)
CRP (> 5 ng/ml)	66 (75)
BMI [kg/m^2]	21.89 ±4.6
Underweight < 18.5 kg/m^2	17 (19.3)
Normal weight 18.5–24.9 kg/m^2	58 (65.9)
BMI > 25 kg/m^2	13 (14.8)

*Continuous variables are reported as mean (m) and standard deviation (SD), CRP – C-reactive, protein, BMI – body mass index. *Information available for only 74 patients.*

Results

According to our inclusion criteria, we found retrospectively MRI examinations of 184 patients with CD, where 96 patients were excluded (MRI of the pelvis – 70 patients; inadequate MRE quality – 9 patients; failed endoscopic evaluation – 10 patients; DWI with a significant artefact – 7 patients) (Figure1). Therefore, 88 patients were finally enrolled in our study.

The baseline characteristics are summarized in Table I. Our study included 41 (46.6%) females, the mean age of the cohort was 38.69 years, and the main part of patients belonged to the A2 age group (with onset of disease between 17 and 40 years). Complications (complicated disease B2 + B3) such as strictures, fistula, and abscess were observed in 43 (48.9%) patients. Almost half of our candidates (n = 51, 58.8%) had conservative therapy; previous abdominal surgery was observed only in 35 (39.8%) patients. The study included 10 current smokers (11.4 %), and the levels of C-reactive protein (CRP) were beyond the upper limit of 5 mg/l for 75% (n = 66). Mostly, we found patients had normal weight (n = 58, 65.9%).

In the next step, we compared the muscle parameters such as mean ADC and mean PMI of both psoas muscles in patients according to each parameter, which defined the disease behaviour and activity (Table II). Analysing the behaviour type, we found a significant difference in ADC between uncomplicated disease (B1, n = 45) and complicated disease (B2 + B3, n = 43) with mean values of 1.11 ±0.19 (10^{-3}*mm^2/s) and 1.03 ±0.10, respectively (p = 0.02). ADC was also significantly higher in non-stricturing patients (n = 51) than in patients with strictures (n = 37) (1.10 ±0.18 and 1.02 ±0.11, respectively, p = 0.01). There was no clinically and statistically significant difference in ADC values in patients with non-penetrating disease vs. penetrating disease (p = 0.65) or patients with vs. without positive CrF (p = 0.44). Also, we did not find any significant difference in patients with low and high MaRIA (p = 0.92). In the assessment of PMI, patients with non-penetrating disease showed clinically higher values than those with penetrating disease (5.71 ±1.88 vs. 4.42 ±1.55 cm^2/m^2, respectively, p = 0.10). According to other parameters such as low and high MaRIA, negative vs. positive creeping fat, uncomplicated disease vs. complicated disease, and non-stricturing vs. stricturing disease, there was no statistical or clinically significant difference.

Table II. Mean apparent diffusion coefficient (ADC) of the psoas muscle and psoas muscle index (PMI)

Variable (mean ± SD)	Uncomplicated disease (behaviour B1) (n = 45)	Complicated disease (behaviour B2 + B3) (n = 43)	P-value
ADC [10^{-3} mm^2/s]	1.11 ±0.19	1.03 ±0.10	0.02
PMI [cm^2/m^2]	5.63 ±1.87	5.61 ±1.91	0.97
	Non-stricturing disease (n = 51)	**Stricturing disease(n = 37)**	
ADC [10^{-3} mm^2/s]	1.10 ±0.18	1.02 ±0.11	0.01
PMI [cm^2/m^2]	5.79 ±1.78	5.81 ±1.91	0.43
	Non-penetrating disease (n = 77)	**Penetrating disease (n = 11)**	
ADC [10^{-3} mm^2/s]	1.07 ±0.17	1.05 ±0.10	0.65
PMI [cm^2/m^2]	5.71 ±1.88	4.42 ±1.55	0.10
	Negative creeping sign (n = 68)	**Positive creeping fat (n = 20)**	
ADC [10^{-3} mm^2/s]	1.08 ±0.15	1.04 ±0.20	0.44
PMI [cm^2/m^2]	5.70 ±1.93	5.37 ±1.71	0.50
	MaRIA < 11 (n = 38)	**MaRIA > 11 (n = 50)**	
ADC [10^{-3} mm^2/s]	1.07 ±0.15	1.07 ±0.17	0.92
PMI [cm^2/m^2]	5.80 ±2.05	5.49 ±1.75	0.45

ADC – mean apparent diffusion coefficient, PMI – psoas muscle index, MaRIA – Magnetic Resonance Index of Activity. Continuous variables are reported as mean (m) and standard deviation (SD).

Intra- and interobserver agreement

The intraobserver and interobserver assessment was performed for evaluating CrF and measuring ADC, PWI, and MaRIA. The obtained results demonstrated excellent agreement (κ = 0.831, ICC more than 0.891, p < 0.05) and are summarized in Supplementary Table SII.

Discussion

To our knowledge, this is the first study to evaluate the association of lumbar muscle ADC values and PMI with CD activity and behaviour. Our results showed a significant difference in ADC values in patients with uncomplicated and complicated disease (p = 0.02), as well as non-stricturing and stricturing diseases (p = 0.01).

In recent years, the prognostic value of body composition parameters in CD patients has been a trending topic. The systematic reviews by Ryan *et al.* and Tang *et al.* reported the incidence of sarcopaenia in approximately 52% of CD, which influenced the inflammatory status, disease behaviour, prognostic outcome, and the effectiveness of drug therapy [6, 25]. According to the current "gut-muscle axis" hypothesis, there is a need to study intramuscular changes, which appear due to the systemic influence of low-grade inflammation in CD patients, to detect earlier the CD forms with poor prognosis [6, 12].

Previous studies have confirmed DWI and ADC efficacy as useful clinical tools to identify the pattern of intramuscular disorders based on changes of free water motion and increasing cellularity [14, 16, 26–32]. Meyer *et al.* in 2018 showed significantly higher muscle ADC values in myositis and myopathy than in unaffected muscles, which was generally related to the appearance of muscle oedema [14]. In subsequent studies, Meyer *et al.* showed a strong correlation between ADC and electromyography findings in myositis, allowing it to reflect a functional muscle condition [32, 33]. Not only structural but also functional changes can be detectable by ADC. For instance, Morvan *et al.* found changes of ADC values after physical exercise due to increased perfusion and delated vascular spaces [34].

For an adequate and standardized comparison of the assessment of muscle loss and the measurement of ADC value, we chose the lumbar muscle due to the low incidence of artefacts, especially on ADC maps, and the simplicity of the measurement method. The assessment of the lumbar muscle loss using PMI showed no significant difference in patients with non-penetrating (B1 + B2) and penetrating disease (B3) (p = 0.10). Zhou *et al.* in 2021 found an association of low muscle-related parameters with complicated disease behaviour (p = 0.048) [35]. Further studies showed a relationship between muscle loss, especially in combination with mesenteric fat index or high visceral fat, and poor outcomes in CD patients [7, 36]. On the other hand, the assessment of ADC values showed significantly lower values in patients with complicated disease compared to uncomplicated or stricturing compared to non-stricturing disease (p = 0.02 and p = 0.01, respectively). Ran *et al.* obtained

lower ADC values in patients with myositis against control groups with unaffected muscles [30]. They explained these changes by the appearance of cytotoxic reactions within the muscle. Another hypothesis was proposed by Dalakas *et al.*, who associated diffusion changes with an increase of cellularity due to the migration of inflammatory cells and also with subsequently intensified inflammatory processes with oedema and necrosis of muscle fibres, and as a result, an increase of the diffusion space for water molecules [37, 38].

The CD activity analysis based on CrF or measuring the MaRIA score did not show any significant difference in ADC or PMI values between all groups. A possible explanation might be the influence of treatment on MaRIA, especially the duration and scheme of treatment, which was not considered. According to the literature, MaRIA correlates with general inflammation parameters such as CRP and mucosal healing, which are highly dependent on the patient's treatment [39–44]. However, we see significant potential in further studies of activity based on MaRIA score and muscle change, because this relationship can improve our knowledge of the systemic influence of bowel inflammation on muscle changes.

Summarizing the obtained results, we see in them a significant clinical value. Firstly, the measurement of ADC values is simple and corresponds to the methodology of assessment of composite parameters of the body. Secondly, the statistically significant difference of muscle ADC values in patients with a complicated and uncomplicated course and between stricturing and non-stricturing behaviour can contribute to identification of CD patients with a worse prognosis. Thirdly, further studies of intramuscular changes based on changes in ADC measurements could potentially lead to identifying CD patients with a lower risk for developing of abscess, fistula, and stricture at an early stage.

Our study has several limitations. It was a monocentric study with a retrospective design. There was no histological conformation of intramuscular changes; thus, distinguishing myositis from other muscle disorders was not possible. Not all patients with penetration complications received MRE; some patients with complications such as perforation or gastrointestinal bleeding required CT examination in the emergency setting. The follow-up time for each scan of the patients was not standardized, and, therefore, follow-up scans were not included in the analysis.

Conclusions

ADC of the psoas muscles is significantly lower in CD patients with uncomplicated disease, particularly those with stricturing disease. Therefore, ADC can be considered as an imaging biomarker of myopathic changes in CD patients.

Acknowledgments

Bohdan Melekh and Felix Barajas Ordonez contributed equally to the manuscript.

Conflict of interest

The authors declare no conflict of interest

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9. Anhang

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Zum Schluss möchte ich diese Arbeit dem ukrainischen Volk widmen, das in einer so schwierigen Zeit für die Freiheit und Unabhängigkeit der Ukraine kämpft. Slava Ukraine.

9.2.Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur

Promotion eingereichte Dissertation mit dem Titel:

„Prognostische Rolle der Magnetresonanz-Enterographie als multiparametrisches radiologisches Verfahren bei Patienten mit Morbus Crohn“

in der Universitätsklinik für Radiologie und Nuklearmedizin

mit Unterstützung durch Herrn Professor 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 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.

Magdeburg, den 22. Dezember 2023

Unterschrift

9.3 Erklärung zur strafrechtlichen Verurteilung

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

Magdeburg, den 22. Dezember 2023

Unterschrift

9.4 Darstellung des Bildungsweges

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