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Inhaltsverzeichnis

Zur besseren Lesbarkeit wird im Folgenden das generische Maskulinum verwendet. Die in dieser Arbeit verwendeten Personenbezeichnungen beziehen sich, sofern nicht anders kenntlich gemacht, auf beide Geschlechter.

Abkürzungsverzeichnis

ATP	Adenosintriphosphat
BMI	Body mass index
CIM	Critical illness myopathy
CIP	Critical illness polyneuropathy
CIPNM	Critical illness polyneuromyopathy
CT	Computertomographie
EMG	Elektromyographie
FOXO	Forkhead box protein O
ICU	Intensive care unit
ICUAW	Intensive care unit acquired weakness
IGF	Insulin-like growth factor
LASSO	Least absolute shrinkage and selection operator
MRC	Medical Research Council
MRT	Magnetresonanztomographie
NCS	Nerve conduction studies
NICU	Neurointensive care unit
NMES	Neuromuskuläre Elektrostimulation
POC	Point of care
QALYs	Quality adjusted life years
MuRF	Muscle RING-finger protein-1
ROS	Reaktive Sauerstoffspezies
SF-36	Short form survey 36
SIRS	Systemic inflammatory response syndrome
TMT	Temporal muscle thickness
TNF	Tumornekrosefaktor
mTor	mechanistic Target of Rapamycin
UP	Ubiquitin-Proteasom

Publikationsliste

Bei der vorliegenden kumulativen Dissertation handelt es sich um eine publikationsbasierte Darstellung der Forschungsergebnisse. Die ausführlichen Ergebnisse wurden bereits in folgenden Fachzeitschriften veröffentlicht:

Schmidbauer, M.L*., **Putz, T***., Gehri, L. *et al.* **Accelerometer-derived movement features as predictive biomarkers for muscle atrophy in neurocritical care: a prospective cohort study**. *Crit Care* **28**, 288 (2024). https://doi.org/10.1186/s13054-024-05067-y

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Bestätigung der Ko-Autoren

Hiermit erkläre **ich**, dass alle beteiligten Koautoren ihr Einverständnis zur Verwendung der folgenden Originalartikel für meine Dissertation gegeben haben.

1. Einleitung

1.1 Definition ICUAW

Intensive care unit acquired weakness (ICUAW) bezeichnet eine neuromuskuläre Dysfunktion, die bei kritisch kranken Patienten im Rahmen der intensivmedizinischen Behandlung auftreten kann und sich klinisch primär als generalisierte Schwäche manifestiert. ICUAW ist als ein heterogenes, klinisches Syndrom zu verstehen und umfasst sich teils überschneidende Pathologien, wie die critical illnes polyneuropathy (CIP), als auch die critical illnes myopathy (CIM) und die cirtical illnes polyneuromyopathy (CIPNM)(1–3).

1.2 Epidemiologie & Prognose

Die mediane Prävalenz der ICUAW wird bei Intensivpatienten mit bis zu 43% angegeben (1). Dabei gibt es erhebliche Unterschiede, je nach Patientenkollektiv und Untersuchungsmethode. Unter anderem ist die Inzidenz bei Patienten mit einer Sepsis höher (4). Das Risiko eine ICUAW zu entwickeln ist von verschiedenen modifizierbaren und nicht-modifizierbaren Faktoren abhängig. Zu den modifizierbaren Risikofaktoren zählen vor allem Hyperglykämie und Immobilisation, sowie parenterale Ernährung und diverse Medikamente (1,5–7). Zu letzteren gehören vor allem Katecholamine, Muskelrelaxantien, Aminoglykoside und Vancomycin (3,8). Es wurde eine Assoziation der ICUAW mit dem Einsatz von Glucocorticoiden berichtet, wobei dies wohl auf deren hyperglykämischen und insulinresistenz-induzierenden Effekte zurückgeht (6,7). Bei Patienten mit stabilen Blutzuckerprofilen unter Insulintherapie wurden sogar protektive Effekte durch Glukokortikoide postuliert (7). Auch Sedativa gehören zu den Risikomedikamenten, wobei hier der Effekt wohl eher auf der durch die Sedierung resultierenden Immobilisation beruht (9). Zu den nicht-modifizierbaren Risikofaktoren gehören das Alter und das weibliche Geschlecht, sowie der funktionelle Status vor Hospitalisierung und die Schwere der Erkrankung (8,10). Hierunter fallen besonders die Dauer der maschinellen Beatmung und das Auftreten von Sepsis, SIRS oder Multiorganversagen (1,4,11). Paradoxerweise konnte in Mausstudien gezeigt werden, dass eine vorbestehende Adipositas protektiv bezüglich der Muskelatrophie im Rahmen der ICUAW ist (12).

Die Entwicklung von ICUAW erschwert den Verlauf der Behandlung und führt zu einem schlechteren Outcome. Unter anderem werden die Beatmungsdauer und sowohl die Zeit auf der Intensivstation, als auch die Dauer der Hospitalisierung verlängert (4). Durch erhöhte 1-Jahres-Mortalität und reduziertes funktionelles Outcome (36-Item Short Form Survey, SF-36) mit damit einhergehende Reduktion der Lebensqualität sind die quality-adjusted life years (QALYs) deutlich verringert (4,4,13).

1.3 Pathophysiologie

Die Pathophysiologie der ICUAW ist komplex, wobei noch nicht alle Pathomechanismen vollständig geklärt sind.

Es wird angenommen, dass Immobilität einen wesentlichen Anteil an der Entwicklung der ICUAW ausmacht. Es gibt diverse klinische Gründe warum Patienten auf Intensivstationen, insbesondere das Subkollektiv mit neurologischen Grunderkrankungen, immobil sind. Hierzu zählen unter anderem vermindertes Bewusstsein, Schädigung von Motoneuronen, kardiovaskuläre Instabilität und Sedierung. Außerhalb der intensivmedizinischen Umgebung konnte bei gesunden Probanden gezeigt werden, dass es durch Nichtgebrauchen der Muskulatur bereits innert einer Woche zu deutlicher Muskelatrophie und Verlust an Muskelkraft (bis zu 5%) kommt (14). Allerdings gibt es Unterschiede zwischen der Muskelatrophie im Rahmen der ICUAW und der Muskelatrophie durch Nichtbenutzen der Muskulatur bei reiner Immobilisierung. In einer Studie konnte gezeigt werden, dass es bei der Immobilisierung mittels Gipses zu einer generalisierten Schwäche und Muskelatrophie kam, aber nicht zu einer Reduktion der Kraft im M. extensor pollicis (15,16). Bei Patienten mit Sepsis kam es jedoch zu einer solchen Kraftminderung (16). Die genauen Gründe hierfür sind noch nicht hinlänglich bekannt. In Studien mit Ratten konnte festgestellt werden, dass die Kombination aus Immobilisierung und kritischer Erkrankung zu einer wesentlich schwerwiegenderen Schädigung der Muskulatur führte, als Immobilisierung allein (17). Ein mögliche Erklärung hierfür könnte die erhöhte Empfindlichkeit des Muskels für Inflammation aufgrund des Wechsels von Typ 1 zu Typ 2 Muskelfasern im Rahmen der verminderten Nutzung der Muskulatur sein (18,19). Des Weitern spielen auch die Zunahme an freien Radikalen, ein veränderter Calciumhaushalt und

eine erhöhte mikrovaskuläre Permeabilität, welche alle durch die Nichtbenutzung der Muskulatur ausgelöst oder verstärkt werden, eine Rolle (20,21).

Darüber hinaus ist der Proteinhaushalt von besonderer Bedeutung. Beim Gesunden besteht ein stabiles Gleichgewicht zwischen Proteinsynthese und Proteinabbau, welches die Funktion der Muskulatur und die Adaptationsfähigkeit des Metabolismus auf plötzliche Veränderungen ermöglicht. Beim älteren Menschen verschiebt sich das Verhältnis hin zu vermehrtem Proteinabbau, was letztendlich zum Verlust von Muskelmasse und im Verlauf zu Sarkopenie führt (1,22). Der Imbalance zwischen Proteinsynthese und Proteinabbau wird bei der Entwicklung der ICUAW eine entscheidende Rolle zugewiesen, da sie den Katabolismus begünstigt. Hierbei spielt der Ubiquitin-Proteasom-Weg (UP) eine zentrale Rolle. Proteine, die abgebaut werden sollen, werden mit Ubiquitin markiert und anschließend von Proteasomen in Aminosäuren aufgespalten. Muskelspezifische Ubiquitin-Ligasen wie Atrogin-1 und Muscle RING-finger protein-1 (MuRF1) sind bei ICUAW stark erhöht und zielen auf strukturelle Komponenten wie dicke Myosinfilamente ab (23–26). Der selektive Verlust dieser Myosinfilamente schwächt den Muskel. Gleichzeitig befördert die Supprimierung des Insulin-like-growthfactors-1 (IGF-1)/Akt/mTOR-Signalweges den Muskelabbau (27). IGF-1, ein wichtiger Wachstumsfaktor für den Muskelerhalt, wird bei ICUAW aufgrund von Inflammation, Immobilität und auch durch Sepsis herunterreguliert, was zu einer verringerten mTOR-Aktivität und niedrigeren Proteinsyntheseraten führt (28). Die Deaktivierung von Akt führt auch zu einer verstärkten Expression von Atrophiefaktoren wie MuRF1 und Atrogin durch die Dephosphorylierung von Forkhead box protein O (FOXO)-Transkriptionsfaktoren (29). Darüber hinaus entwickelt sich bei ICUAW eine anabole Resistenz, bei der das Muskelgewebe nicht auf anabole Signale reagiert oder die verfügbaren Aminosäuren nicht effektiv verwertet. Als Grund dafür wird eine mikrovaskuläre Dysfunktion vermutet, die die Zufuhr von Nährstoffen und Sauerstoff zum Muskel verringert (20).

Ein weiteres Merkmal der ICUAW ist die Verringerung der Kontraktionsfähigkeit der Muskulatur, die häufig einem erkennbaren Verlust an Muskelmasse vorausgeht. Dieses Phänomen ist eng mit strukturellen Störungen innerhalb der Muskelfasern verbunden. Die Myofilamente, die aus Aktin und Myosin bestehen, sind ein wesentlicher Bestandteil der Muskelkontraktion. ICUAW geht mit einem Abbau der Integrität der Myofilamente einher, der in erster Linie auf die Aktivität von

proteolytischen Enzymen wie Calpainen und Caspasen zurückzuführen ist. Calpaine, die durch erhöhte intrazelluläre Kalziumspiegel aktiviert werden, bauen Strukturproteine ab und hemmen die Akt-Signalübertragung, wodurch die Proteinsynthese beeinträchtigt wird. In ähnlicher Weise tragen Caspasen, insbesondere Caspase-3, zur Proteolyse und Apoptose bei, wodurch die Muskelfasern weiter geschwächt werden (30–32).

Die Dysfunktion des sarkoplasmatischen Retikulums spielt eine entscheidende Rolle bei ICUAW. Es kommt zu einer verminderten Kalziumfreisetzung und einer Dysbalance im intrazellulären Calciumhaushalt, was Calpaine und andere proteolytische Wege aktiviert. Diese Kalziumungleichgewichte mindern nicht nur die Kontraktilität, sondern beschleunigen auch den Proteinabbau. Die verminderte elektrische Erregbarkeit verstärkt die Muskelfunktionsstörung bei ICUAW weiter. Veränderungen in der Natriumkanalexpression, einschließlich der Hochregulierung der embryonalen Nav1.5-Isoform, stören die Membranpolarisation und machen die Muskelfasern unfähig, sich zu bewegen. Dies führt zu einer funktionellen Denervierung und weiterem Muskelschwund (32–34).

Mitochondriale Dysfunktion und oxidativer Stress sind ebenfalls von zentraler Bedeutung für die Pathogenese der ICUAW. Mitochondrien, die primären Energieproduzenten in Muskelzellen, sind bei ICUAW stark beeinträchtigt, was zu einer verminderten Adenosintriphosphat(ATP)-Produktion und einer Anhäufung reaktiver Sauerstoffspezies (ROS) führt. Der durch die Sepsis ausgelöste oxidative Stress schädigt die mitochondrialen Komponenten, wodurch ihre Funktion weiter beeinträchtigt wird und so ein Teufelskreis aus Energiemangel und erhöhter ROS-Bildung entsteht. Was wiederum Muskelfasern schwächt und die Proteolyse beschleunigt. Freie Radikale tragen auch zum Abbau von Myofilamenten und zur Aktivierung von proteolytischen Enzymen wie Calpainen und dem UP-Weg bei. Zytokine, einschließlich des Tumornekrosefaktors alpha (TNF-α), verstärken diese Auswirkungen, indem sie die IGF-1-Signalübertragung beeinträchtigen und die Proteolyse fördern (32,33).

Des Weiteren ist Myostatin, ein Regulator des Muskelwachstums, bei ICUAW erhöht und verstärkt atrophische Signalwege. Hyperglykämie und Insulinresistenz, die bei kritisch kranken Patienten häufig vorkommen, beeinträchtigen die

Glukoseaufnahme und ATP-Produktion in den Muskelzellen zusätzlich und verstärken den oxidativen Stress in der Zelle. Zusammen sind diese molekularen Pathomechanismen für die komplexe Schädigung der Muskelstruktur und -funktion verantwortlich, was die Herausforderungen bei der Entwicklung gezielter Therapien unterstreicht (1,32).

1.4 Diagnostik

Die empfohlene Standardmethode zur Diagnostik der ICUAW ist die klinische Untersuchung der Muskelfunktion, in deren Rahmen der summierte Medical Research Council (MRC) Score erhoben wird. Der MRC bewertet die Muskelkraft mit 0 (keine Kontraktion) bis 5 Punkten (normale Muskelkraft) beidseitig für 12 verschiedene Muskelgruppen. Dabei reicht die Skala von 0 bis 60. Bei <48 Punkten kann eine ICUAW diagnostiziert werden (4). Um den MRC zu erheben ist man allerdings auf einen wachen und kooperationsfähigen Patienten angewiesen, außerdem schränkt eine bestehende Hemiparese durch einen Schlaganfall oder anderweitige vorausgegangene Hirnschädigung die Vergleichbarkeit hinsichtlich der generalisierten Muskelatrophie mit Patienten ohne fokal neurologisches Defizit ein. Die Verwendung bei sedierten, schwerkranken, komatösen aber auch Patienten mit akuter Gehirnschädigung ist daher limitiert. Außerdem lässt sich vom MRC nicht auf die Ätiologie der Muskelschwäche schließen. Die Reproduzierbarkeit wird als gut beschrieben, wobei es auch Arbeiten gibt, in den dies nicht bestätigt werden konnte (35–37). Einen weiteren quantitativen Marker stellt die Messung der Handgriffkraft mittels Hand-Dynamometer dar. Nachteil ist, dass es hierzu, wie auch beim MRC eines wachen, kooperationsfähigen Patienten bedarf. Außerdem wird die Generalisierbarkeit dieser Methode auf die allgemeine Muskelkraft angezweifelt (38,39). Die diagnostischen Verfahren, die Muskelfunktion und -kraft untersuchen, können nicht zwischen CIP und CIM unterscheiden. Aus diesem Grund bieten sich elektrophysiologische Verfahren wie die Elektromyographie (EMG), Nervenleitgeschwindigkeit und direkte Muskelstimulation als zusätzliche Untersuchungen an. Nachteil ist hierbei, dass diese Untersuchungen zeitaufwendig sind und eines erfahrenen Untersuchers bedürfen. Hinzu kommt, dass die Durchführung aufgrund von Ödemen oftmals schwierig ist (3,40).

Weitere diagnostische Ansätze wie Muskel- und Nervenbiopsien oder bioelektrische Impedanzmessungen werden seltener angewandt. Erstere aufgrund der Invasivität und der zu komplexen Aufarbeitung der Proben im klinischen Alltag (41,42). Letzteres aufgrund der starken Beeinflussungen der Untersuchungsmethode durch Ödeme und die Hauttemperatur (4).

Aufgrund der diversen Einschränkungen der oben diskutierten diagnostischen Methoden, wurden bereits diverse bildgebende Verfahren als Surrogat Marker bzw. ergänzende Modalitäten evaluiert. CT und MRT eignen sich gut dafür die Infiltration von Muskeln durch Fettgewebe, selbst bei Patienten mit massiven Wassereinlagerungen, sehr genau und zuverlässig zu bestimmen. Jedoch ist es im klinischen Alltag aufgrund von hohen Kosten und Zeitaufwand, zusätzlichen Transporten und im Falle der Computertomographie auch Strahlenbelastung nicht vertretbar diese Modalitäten routinemäßig als Monitoringmethode einzusetzen (3,4).

Es ist daher naheliegend das die Sonographie als universell verfügbares, praktisch nebenwirkungsfreies und kostengünstiges Point of care (POC) Verfahren vermehrt zur Diagnostik der ICUAW herangezogen wird. Hierbei können sowohl qualitative (Muskelstruktur) als auch quantitative Aspekte (Muskelmasse) der Muskulatur beurteilt werden. Am verbreitetsten ist die Verwendung des Durchmessers und der Fläche des Musculus quadriceps femoris als Surrogate für die Muskelatrophie (43). Alternativ dazu wurde an der oberen Extremität der Musculus biceps brachii evaluiert, was sich allerdings nicht als ideal erwies, da die untere Extremität proportional deutlich stärker von der Muskelatrophie durch Immobilität betroffen ist (44). Zur qualitativen Beurteilung der Echogenität kann zusätzlich der Heckmatt-Score herangezogen werden, der gut mit der Störung der Muskelarchitektur korreliert (45). Trotz der vielen Vorteile birgt die Sonographie auch diverse Nachteile und Einschränkungen. Hierzu zählt, dass die Untersuchung stark Anwenderabhängig ist und außerdem von der Lagerung des Patienten abhängt. Es bedarf bei den Folgeuntersuchungen eines Platzierens der Sonde an der exakt gleichen Stelle wie bei der Voruntersuchung. Die Sonde muss mit minimalem Druck und ausreichend Ultraschallgel verwendet werden. Der Muskeldurchmesser unterschätz außerdem gegenüber der Fläche die Muskelatrophie. Darüber hinaus wird der Ultraschall auch durch Ödeme und Adipositas beeinträchtigt (3,46,47).

Es zeigt sich, dass jede Modalität Stärken und Schwächen hat. Im Alltag auf der Intensivstation bietet es sich daher bei der Diagnostik der ICUAW eine multimodale, an den Zustand des Patienten angepasste Herangehensweise an. Ziel ist es möglichst schonend und frühzeitigen eine Diagnose zu stellen, um so schnell und intensiv intervenieren zu können und damit das Auftreten einer ICUAW zu verhindern beziehungsweise die Folgen des Syndroms zu mildern.

1.5 Monitoring der Entwicklung und der Risikofaktoren einer ICUAW

Mit den im vorherigen Absatz beschriebenen Methoden lässt sich zwar die Diagnose ICUAW stellen, allerdings gibt es keinen definierten Standard zu welchem Zeitpunkt und wie oft die Untersuchungen stattfinden sollen, so dass die Diagnose am Ende immer klinisch getroffen werden muss. Deswegen stellt das Monitoring der Entwicklung einer ICUAW auf der Intensivstation eine Herausforderung dar. Hierbei konnten bisweilen longitudinale Ultraschallmessungen vor allem des M. rectus femoris als zuverlässige Marker für die Muskelatrophie im Verlauf des Intensivaufenthalts etabliert werden (43).

Weitere Risikofaktoren und Biomarker, die bei der Entwicklung einer ICUAW eine Rolle spielen, wie der Blutzuckerspiegel, systemische Inflammation und die kumulative Menge applizierter Risikomedikamente zur Sedierung oder Relaxierung werden auf Intensivstationen in der Regel bereits engmaschig überwacht. Außerdem kann der tatsächliche Ruheenergiebedarf durch indirekte Kalorimetrie überwacht werden, um eine adäquate Ernährung zu gewährleisten und schädliche hyperkalorische Zustände in der Akutphase der Erkrankung zu vermeiden.

Wie schon im Kapitel Pathophysiologie beschrieben, stellt die Immobilität einen weiteren wichtigen Faktor bei der Entwicklung der ICUAW dar. Um die aktive Bewegung, d.h. diejenigen Bewegungen, die der Patient aus eigener Kraft gegen die Schwerkraft durchführt und nicht die passive Bewegung wie Physiotherapie, Lagerung, Transporte oder die Verwendung des „Bettfahrrads“ zu quantifizieren gibt es verschieden Möglichkeiten: Dokumentation auf Basis von Beobachtungen des Pflege- und Therapiepersonals, kontinuierliche Videodokumentation oder Aufzeichnung der Aktivität mittels Bewegungssensoren (44). Da einige dieser Methoden nicht standardisiert sind und teils auch nicht einfach durchzuführen sind wurden in bisherigen Studien Bewegung als Confounder der ICUAW oder

des Outcomes in Ernährungsstudien in der Regel nicht berücksichtigt. Eine Lösung könnten hier handelsübliche Bewegungssensoren darstellen. Sie sind kleiner als eine Streicholzschachtel und können Beschleunigung in den drei Raumebenen kontinuierlich aufzeichnen. Hierbei kann die Empfindlichkeit in Abhängigkeit zur Erdbeschleunigung (g = 9,81m/s) sowie die Abtastrate pro Sekunde (Hz) festgelegt werden. Wobei letztere die maximale Aufzeichnungsdauer bezüglich der Faktoren Speicherplatz und Akkulaufzeit begrenzt. Bei einer Abtastrate von 10 Hz je nach Modell mindestens für eine Dauer von 14 Tagen aufgezeichnet werden kann. Beschleunigungssensoren sind außerhalb des medizinischen Bereichs bereits weit verbreitet u.a. in Smartphones und Fitness-Trackern (45). Im medizinischen Bereich wurden bereits von Connolly et al. bei einem älteren Patientenkollektiv einer Tagesklinik demonstriert, dass sich Bewegungssensoren dazu eignen die körperliche Aktivität im Alltag aufzuzeichnen und dabei eine geringe aufgezeichnete körperliche Aktivität mit einem erhöhten Risiko für Muskelatrophie einhergeht (46). Auch auf Intensivstationen wurden Bewegungssensoren bereits erfolgreich für verschiedene Anwendungsszenarien getestet: Hierunter zählen verschiedene Bewegungsereignisse, neurologische Zustände, Delir, Sedierung und Schlafanalyse (47–49). Dabei konnte in allen Bereichen eine gute Korrelation zwischen den Daten der Sensoren und den von Beobachtern dokumentierten Bewegungen nachgewiesen werden. Der Einsatz von Bewegungssensoren wird außerdem als sicher und im Kontext der Intensivstation als gut durchführbar beschrieben (50,51). Der große Vorteil dieser Technologie ist die kontinuierliche, nicht-invasive und personalunabhängige Aufzeichnung aller Patientenbewegungen. Perspektivisch könnten die Daten in Zukunft in ein tagesaktuelles Vorhersagemodell einfließen, um zusammen mit sequenziellen Ultraschallmessungen und neurophysiologischen Methoden eine individuellere Prognose und potenziell frühzeitigere Interventionen zu ermöglichen (49).

1.6 Therapie

Es gibt aktuell keine wirksame Therapie für die ICUAW. Daher muss primär auf Prävention gesetzt werden. Zu den wichtigsten Präventionsmaßnahmen gehören die frühzeitige Erkennung und Behandlung der Sepsis. Dies mildert nicht nur die durch Inflammation verursachten Muskelschäden, sondern erleichtert auch der frühzeitige Beginn der Wiederherstellung der körperlichen Funktion, wodurch das

Auftreten von Muskelschwäche verringert wird. Eine strenge Kontrolle des Blutzuckerspiegels verringert zwar die Entwicklung von CIP/CIM und prolongierten Beatmungsdauern, ist aber auch mit einem erhöhten Hypoglykämierisiko und einer höheren Sterblichkeit assoziiert (6,7,48). Die optimalen Blutzuckerwerte sind nach wie vor umstritten. Darüber hinaus ist die Art der Ernährung von Bedeutung, wobei eine frühzeitige enterale Ernährung der parenteralen Ernährung vorzuziehen ist, die mit einem höheren Risiko für ICUAW, einer verzögerten Genesung und einer verlängerten mechanischen Beatmung sowie einem längeren Aufenthalt auf der Intensivstation verbunden ist (49,50).

Immobilisierung zu vermeiden, ist ein weiterer Baustein in der Prävention der ICUAW. Dies kann sowohl durch einen restriktiveren Einsatz von Sedativa, als auch durch frühzeitige Mobilisierung und den Einsatz von elektrischer Muskelstimulation geschehen (51–53). Allerdings ist die Literatur diesbezüglich nicht eindeutig und die Frage, ob ICUAW so verhindert werden kann noch nicht abschließend geklärt (54). In einem aktuellen Review konnte festgestellt werden, dass frühe Mobilisierung auf Intensivstationen sicher und gut durchführbar ist. Frühmobilisierung führte zu reduzierter Muskelatrophie, verbesserter Muskelkraft, kürzerer Beatmungsdauer, verkürzter Hospitalisierungsdauer, weniger beatmungsassoziierten Pneumonien sowie zu verbesserter Blutzuckerregulierung und verminderter Inflammation (55–57). Andere Studien konnten jedoch keinen Überlebensvorteil bei Patienten mit reduzierter Sedierung und intensivierter Frühmobilisierung feststellen. In der Interventionsgruppe kam es sogar vermehrt zu Komplikationen (58).

Die neuromuskuläre Elektrostimulation (NMES) wird als potenzielle alternative Therapie untersucht, insbesondere für Patienten, die nicht aktiv an der körperlichen Rehabilitation teilnehmen können. Es konnte gezeigt werden, dass die Ergänzung der Frühmobilisierung durch NMES die Inzidenz von ICU-AW verringern, die Muskelkraft verbessern und den Krankenhausaufenthalt verkürzen kann (59,60). Jüngste systematische Übersichten und Metaanalysen haben jedoch widersprüchliche Ergebnisse in Bezug auf die Auswirkungen auf die Muskelkraft, die Dauer der mechanischer Beatmung und des Aufenthalts auf der Intensivstation gezeigt (61,62).

1.7 Relevanz der ICUAW in der neurologischen Intensivmedizin

Für die neurologische Intensivmedizin ist die Differenzialdiagnose der ICUAW besonders anspruchsvoll und relevant, da die Symptome der ICUAW häufig mit den primären neurologischen Erkrankungen überlappen können. Hinzu kommt die Tatsache, dass die betroffenen Patienten aufgrund von motorischen Defiziten, Enzephalopathie oder lang andauernder Sedierung oft über einen längeren Zeitraum immobilisiert sind, was einen der größten Risikofaktoren für die ICUAW nochmals verstärkt (63).

1.8 Fragestellung und Studiendesign

Das Ziel dieser Arbeit ist es, diagnostische und prädiktive Methoden für das Management der ICUAW zu erforschen und zu validieren. Die Forschung konzentriert sich auf zwei Fragen:

1. Können von Beschleunigungsmessern aufgezeichnete Beschleunigungsdaten als prädiktiver Biomarker für Muskelschwund dienen, und wie kann dies in die individualisierte Patientenversorgung mit einbezogen werden?
2. Kann der Durchmesser des M. temporalis, gemessen mittels Ultraschall oder Kopf-CT, als neuer, zuverlässiger Biomarker alternativ zum Durchmesser des M. rectus femoris, als Goldstandard der Messung von Muskelatrophie in der NICU-Kohorte verwendet werden?

Hierzu wurden zwei monozentrische, prospektive Kohortenstudien auf einer neurologischen Intensivstation durchgeführt. Das Patientenkollektiv wurde nach strengen Auswahlkriterien bezüglich vor Aufnahme bestehender Sarkopenie selektiert. Es erfolgte eine engmaschige Dokumentation einer breiten Zahl an Confoundern und verschiedener Bildgebungsmodalitäten um ein möglichst detailliertes Bild über die klinische Phase, in der sich die ICUAW bei kritisch Kranken entwickelt, zu erhalten. Bei der Auswertung wurden mit Hilfe eines LASSO-Modells (least absolute shrinkage and selection operator) die nicht relevanten unabhängigen Kovariablen aussortiert, so dass anschließen mit Hilfe eines Regressionsmodell die relevanten Einflussfaktoren auf die Muskelatrophie als Endpunkt untersucht werden konnten. Außerdem wurde zum Vergleich der verwendeten Bildgebungsmethoden ein Bland-Altmann Diagramm und der Intraklassenkorrelationskoeffizient verwendet.

1.9 Beitrag der Publikation: „Diagnostic Utility of Temporal Muscle Thickness as a Monitoring Tool for Muscle Wasting in Neurocritical Care" zu den aktuellen Forschungsfragen im Bereich ICUAW

In dieser Arbeit wird der Durchmesser des M. temporalis (TMT) als Biomarker für Muskelatrophie bei neurologischen Intensivpatienten als Surrogat Marker für I-CUAW untersucht. Diese Studie möchte eine Möglichkeit zur bettseitigen, praktikablen Diagnostik und Überwachung der Muskelatrophie bei kritisch kranken Patienten, bei denen die standardmäßigen Muskelfunktionstests nicht durchführbar sind, untersuchen. Durch die Untersuchung der Korrelation zwischen TMT und traditionelleren Muskeldickenmessungen, belegt diese Untersuchung die klinische Validität von TMT-Messungen als gutes Surrogat zum M. rectus femoris. Außerdem zeigte sich die Ultraschallmethode als Gleichwertig zur Messung des TMT im CT. Die Ergebnisse betonen den Wert der TMT als einfaches und gut reproduzierbares Instrument zur Erkennung der ICUAW.

1.10 Beitrag der Publikation: "Accelerometer-derived movement features as predictive biomarkers for muscle atrophy in neurocritical care: a prospective cohort study" zu den aktuellen Forschungsfragen im Bereich ICUAW

Diese Veröffentlichung untersucht die Möglichkeit aus Bewegungsdaten von Beschleunigungssensoren Prädiktoren für die Muskelatrophie bei ICUAW abzuleiten. Körperliche Inaktivität ist eine der Hauptursachen für Muskelatrophie und I-CUAW auf der Intensivstation, das genaue Ausmaß war allerdings aufgrund fehlender Biomarker bisher schwer zu quantifizieren. Es wird untersucht, ob sich Bewegungssensoren praktikabel über einen längeren Zeitraum zur Überwachung der Patientenbewegungen einsetzen lassen. So wird erstmals das genaue Ausmaß der aktiven Patientenbewegung während des Intensivaufenthalts quantifiziert. Außerdem wird mit Hilfe von maschinellem Lernen ein Modell erstellt, dass den Anteil der Muskelatrophie, der durch Immobilität entsteht unter Berücksichtigung diverser anderer klinischer Parameter genauer einschätzt.

2. Zusammenfassung:

Körperliche Inaktivität und die daraus resultierende Muskelatrophie sind bei schwerkranken Patienten weit verbreitet und tragen erheblich zur ICUAW bei.

Dabei machen die hohen Folgekosten, erhöhte Komplikationsraten und schwerwiegenden Langzeitfolgen sowie eine erhöhte 1-Jahres Mortalität die ICUAW zu einem hoch relevantem Forschungsschwerpunkt.

Bislang hat das Fehlen quantifizierbarer Biomarker für Inaktivität die Untersuchung der sonstigen Einflussfaktoren von ICUAW erschwert und die Forschung auf diesem Gebiet verkompliziert.

Außerdem fehlt eine einfache bettseitige Diagnostikmethode, die unabhängig von der Körperzusammensetzung bzw. Körperfettanteil des Patienten oder etwaiger Wassereinlagerung ist und gleichzeitig Aussagen über die generalisierte Muskelatrophie zulässt.

Unsere Hypothese ist, dass aktive Bewegung, gemessen mit nicht-invasiven, am Körper befestigten Beschleunigungsmessern, als zuverlässiger Indikator für das Aktivitätsniveau dienen und zur Vorhersage von Muskelatrophie beitragen könnte. Mit Hilfe von maschinellem Lernen entwickelten wir ein Modell, um diese Hypothese zu testen.

Die 2. Hypothese ist, dass sich der Durchmesser des M. temporalis gemessen im cCT und im Ultraschall als neuer, alternativer Biomarker für die Muskelatrophie bei ICUAW zur Standardmethode (Durchmesser des M. rectus femoris) eignet.

Wir konnten dabei zeigen, dass sich neurologische Intensivpatienten während ihres Aufenthalts auf der Intensivstation weniger als 1 % der Zeit aktiv bewegen und das Aktivitätsniveau bei nur etwa 6 % des Aktivitätsniveaus gesunder Personen liegt. Außerdem konnte unser Modell bestätigen, dass der Anteil der aktiven Bewegung ein messbarer Biomarker für die Vorhersage von Muskelatrophie, während eines Intensivaufenthalts nach 10 Tagen ist.

Außerdem zeigten wir, dass der Durchmesser des M. temporalis gemessen im cCT und im US als einfaches und gut reproduzierbares Instrument zur Erkennung der ICUAW geeignet ist.

Daraus folgende Implikationen für Forschung und Praxis:

Die Einbeziehung von aus Beschleunigungssensoren abgeleiteten Biomarkern verbessert die Vorhersage von Muskelatrophie bei neurologischen Intensivpatienten. Dieser Fortschritt ebnet den Weg für eine bessere Phänotypisierung von ICUAW und unterstützt die Entwicklung maßgeschneiderter Interventionen. Künftige Studien zu ICUAW sollten diese Biomarker als Kovariablen berücksichtigen.

Die Verwendung des M. temporalis als alternativer Messort zur Evaluation der ICUAW sollte unbedingt bedacht werden, insbesondere bei Patienten, bei denen der M. rectus femoris nicht zuverlässig herangezogen werden kann.

3. Abstract (English):

Physical inactivity and the resulting muscle atrophy are widespread in critically ill patients and contribute significantly to ICUAW.

The high follow-up costs, increased complication rates and serious long-term consequences as well as increased 1-year mortality make ICUAW a highly relevant research focus.

To date, the lack of quantifiable biomarkers for inactivity has hampered the assessment of ICUAW and complicated research in this field.

In addition, a simple bedside diagnostic method that is independent of the patient's body composition or body fat percentage or fluid retention and at the same time allows the approximation of generalized muscle atrophy is lacking

Our hypothesis is that active movement, measured with non-invasive accelerometers attached to the body, could serve as a reliable indicator of activity levels and contribute to the prediction of muscle atrophy. Using machine learning, we developed a model to test this hypothesis.

The second hypothesis is that the thickness of the temporalis muscle is suitable as a new, alternative biomarker for muscle atrophy in ICUAW to the standard method (thickness of the rectus femoris muscle).

We were able to show that neurological ICU patients are active less than 1 % of the time during their stay in the ICU and reach only about 6 % of the activity level of healthy patients.

Furthermore, our model confirmed that the percentage of active movement is a suitable biomarker for the prediction of muscle atrophy after 10 days during an intensive care stay.

Additionally, we showed that the diameter of the temporalis muscle is a simple and reproducible tool for the detection of ICUAW.

Implications for further research and clinical practice:

The inclusion of accelerometer-derived biomarkers improves the prediction of muscle atrophy in neurological intensive care patients. These findings pave the

way for better phenotyping of ICUAW and supports the development of customized interventions. Future studies on ICUAW should consider these biomarkers as covariates.

The use of the temporalis muscle as an alternative site for the evaluation of ICUAW should be considered, especially in patients in whom the rectus femoris muscle cannot be utilized reliably.

4. Originalarbeit I

Meine Eigenleistung an folgender Publikation bestand in der Literaturrecherche, Mitgestaltung des Studienprotokolls und Durchführung verschiedener Vorversuche zur Etablierung der Bewegungssensoren im Stationsalltag zweier Intensivstationen. Darüber hinaus war ich für die Patientenrekrutierung und die selbständige Durchführung aller beschriebenen Methoden und auch die Einarbeitung einiger Co-Autoren in diese, sowie für die Erhebung des 3-Monate Follow-ups verantwortlich. Ich pflegte die Studiendatenbank und war für die Qualitätskontrolle der erhobenen Daten mitverantwortlich. Außerdem bereitete ich die Daten für die statistischen Analysen auf. Die erste Fassung der Publikation wurde von mir eigenständig verfasst und von meinen Co-Autoren Korrektur gelesen und verbessert.

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Accelerometer-derived movement features as predictive biomarkers for muscle atrophy in neurocritical care: a prospective cohort study

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Abstract

Background Physical inactivity and subsequent muscle atrophy are highly prevalent in neurocritical care and are recognized as key mechanisms underlying intensive care unit acquired weakness (ICUAW). The lack of quantifiable biomarkers for inactivity complicates the assessment of its relative importance compared to other conditions under the syndromic diagnosis of ICUAW. We hypothesize that active movement, as opposed to passive movement without active patient participation, can serve as a valid proxy for activity and may help predict muscle atrophy. To test this hypothesis, we utilized non-invasive, body-fixed accelerometers to compute measures of active movement and subsequently developed a machine learning model to predict muscle atrophy.

Methods This study was conducted as a single-center, prospective, observational cohort study as part of the MINCE registry (metabolism and nutrition in neurointensive care, DRKS-ID: DRKS00031472). Atrophy of rectus femoris muscle (RFM) relative to baseline (day 0) was evaluated at days 3, 7 and 10 after intensive care unit (ICU) admission and served as the dependent variable in a generalized linear mixed model with Least Absolute Shrinkage and Selection Operator regularization and nested-cross validation.

Results Out of 407 patients screened, 53 patients (age: 59.2 years (SD 15.9), 31 (58.5%) male) with a total of 91 available accelerometer datasets were enrolled. RFM thickness changed − 19.5% (SD 12.0) by day 10. Out of 12 demographic, clinical, nutritional and accelerometer-derived variables, baseline RFM muscle mass (beta − 5.1, 95% CI − 7.9 to − 3.8) and proportion of active movement (% activity) (beta 1.6, 95% CI 0.1 to 4.9) were selected as significant predictors of muscle atrophy. Including movement features into the prediction model substantially improved performance on an unseen test data set (including movement features: $R^2 = 79\%$; excluding movement features: $R^2 = 55\%$).

Conclusion Active movement, as measured with thigh-fixed accelerometers, is a key risk factor for muscle atrophy in neurocritical care patients. Quantifiable biomarkers reflecting the level of activity can support more precise phenotyping of ICUAW and may direct tailored interventions to support activity in the ICU. Studies addressing the external validity of these findings beyond the neurointensive care unit are warranted.

Trial registration DRKS00031472, retrospectively registered on 13.03.2023.

Keywords ICU, ICUAW, Sarcopenia, Muscle atrophy, Accelerometer, Machine learning

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Background

Intensive care unit acquired weakness (ICUAW) describes a neuromuscular dysfunction secondary to critical illness and its treatment with consecutive generalized weakness. Data on prevalence for ICUAW show considerable variation due to diverse patient demographics and heterogenous methodology. However, with a systematic review pinpointing the median prevalence at 43% [1], its ubiquity in critical care is evident. Moreover, the impact resulting from ICUAW is profound and long-lasting, with patient outcomes significantly compromised for up to five years after discharge [2–6]. Therefore, ICUAW is acknowledged as a key component of post intensive care syndrome (PICS), highlighting its importance in the continuum of long-term recovery following critical care [7, 8].

ICUAW needs to be recognized as a clinical syndrome, rather than a specific disease entity. As such, it exhibits great heterogeneity and partially overlapping pathologies, which has diluted research findings and made the identification of treatable targets challenging in the past [9–12]. Relevant and common entities include critical illness myopathy (CIM), critical illness polyneuropathy (CIP) as well as critical illness polyneuromyopathy (CIPNM) as an overlap syndrome [9, 11, 12]. Electrophysiological methods including nerve conduction studies (NCS), electromyography and direct muscle stimulation have been successfully used to establish biomarkers for CIM, CIP and CIPMN [9, 13, 14]. Muscle atrophy due to mechanical unloading is also being recognized as a critical component of ICUAW. However, measurable biomarkers to assess the extent of inactivity of muscles are lacking.

In this regard, it is important to note that activity arises from active movement, as opposed to passive movement during mobilization without active patient participation. Hence, we postulate that establishing a proxy for activity can be achieved by applying non-invasive, body-fixed accelerometers to the lower extremities of critically ill patients while prospectively excluding episodes with passive mobilization such as intrahospital transports, physiotherapy and patient positioning. By introducing these biomarkers as continuous measures of active movement and incorporating these variables into a machine learning model, we aimed to predict rectus femoris muscle atrophy, as measured by ultrasound up to day 10 of intensive care unit (ICU) treatment. Based on the hypothesis that neurocritical care patients exhibit a higher prevalence of inactivity due to disorders of consciousness and motor deficits, we specifically included patients with acute brain injury in this trial.

Methods

Study design, setting and clinical management

This study was designed as a single-center, prospective, observational cohort study as part of the MINCE registry (metabolism and nutrition in neurointensive care, DRKS-ID: DRKS00031472, retrospectively registered on 13.03.2023) at a tertiary academic center (LMU University Hospital, Munich, Germany). Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. This study was approved by the local ethics committee (LMU Munich, project number 22-0173, 11.04.2022). Written consent was obtained from all participants or their next of kin. The study recruited from April 2022 to March 2024 and included patients within 48 h after ICU admission with age $\geq$ 18 years, neurologic disease as admitting diagnosis, and expected ICU length of stay $\geq$ 10 days. Patients with pre-existing neuromuscular disease, renal replacement therapy, pregnancy, pre-existing neoplastic disease, recent hospitalization (hospital stays longer than three days in the last three months, ICU treatment within the last three months), pre-existing confinement to bed, and pre-existing frailty (Clinical Frailty Scale > 3) were excluded.

Patients were mobilized at the treating physicians' discretion. If indicated, patients received physiotherapy for 20–40 min/day on six days of the week and were repositioned and transferred from bed to chair regularly by the nursing staff. Nutritional therapy was conducted according to the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines, with caloric and protein targets of 25 kcal/kg/day and 1.3 g/kg/day, respectively [15]. As a reference, body weight as measured with bed scales was used for non-obese patients, and ideal body weight was used for patients with a body mass index (BMI) > 30 kg/m^2 [15]. During the acute phase of illness (days 1–3), hypocaloric nutrition (70% of energy expenditure (EE)) was aimed for. From day 4 on, isocaloric (100% of EE) nutrition was implemented.

Data collection

Clinical data prospectively collected on the ICU included age, sex, body mass index (BMI), admission diagnosis, cumulative protein and calorie deficit, duration of mechanical ventilation, ICU length of stay (LOS), daily Sepsis-related Organ Failure Assessment score (SOFA) and SOFA without Glasgow Coma Scale (GCS) score (mSOFA), Acute Physiology and Chronic Health Evaluation (APACHE II) score on ICU admission, Nutrition

Risk in Critically ill score (NUTRIC) on admission, premorbid modified Rankin Scale (pmRS) and Glasgow Outcome Scale Extended (GOSE) at ICU discharge.

Ultrasound of the upper thigh (rectus femoris muscle, RFM) and temporalis muscle (TM) was performed bilaterally using a 20 MHz linear probe (MyLabOmega, Esaote, Genoa, Italy) upon admission, and on days 3, 7 and 10. As previously described [16, 17], the site of measurement for RFM was marked in the lower third of the connecting line between the anterior superior iliac spine and the upper edge of the patella with a permanent marker to ensure reproducibility between measurements (Supplementary Fig. 1). Measurements were conducted according to a local protocol that emphasized minimal compression during RFM sonography and called for individual adjustments of depth and gain to optimally visualize the surface of the femur and to delineate fascial borders, respectively. Measurement of TM followed the protocol as described by Maskos et al. [17] Three repeated measurements were performed by one of six raters (TP, LG, LR, AM, JB, SI), using the built-in software of the ultrasound machine to measure muscle thickness. The mean value of the repeated measurements was used for further analysis. Reliability of repeated ultrasound measurements is reported in Supplementary Table 1.

Tri-axial accelerometers (range ± 16 g; sampling rate 12.5 Hz; Axivity Ltd., Newcastle upon Tyne, UK) were attached within 48 h of admission to both upper thighs with transparent adhesive tape. Skin inspections and minor adjustments to the sensor placement were performed every third day to prevent any pressure damage. To exclude any passive movement not contributing to the patient's activity, episodes with physiotherapy, intrahospital transports, or repositioning by nursing staff were prospectively documented and excluded from the recorded data. The sensor data was extracted and analyzed by an author (MW) not involved in the patients' clinical management and blinded for the ultrasound measurements.

As a positive control, accelerometers were attached to healthy individuals (n = 3). Static placement of sensors served as a negative control (Supplementary Table 2).

Accelerometer data processing

OmGUI version 1.0.0.11 software was used to download the raw acceleration data from the devices. MATLAB (Mathworks Inc., Natick, USA, release R2022a, version 9.12.0) was used for data processing. Periods of active movement were identified following a previously established procedure that has been already used for activity recognition in ICU settings [18, 19]. Accordingly, recorded time series from each axial component (x, y, z) were first down-sampled to 10 Hz and subsequently high-pass filtered (4th order Butterworth filter, cutoff frequency at 0.2 Hz) to remove baseline offset and low-frequency effects reflecting static postural orientation. Filtered time series were segmented into non-overlapping 5 s windows for subsequent motion feature extraction. Signal magnitude area (SMA) was then computed for every window [19] to identify activity bouts (AB) using a defined threshold of SMA ≥ 0.135 g [18]. Across all identified AB, the mean intensity (AB-intensity) and duration (AB-duration) as well as the variability (standard deviation, SD) of these features were calculated. The distribution of motion features across ABs is log-normal, which required estimating mean and SD via a maximum likelihood technique [20]. The overall movement intensity, the proportion of active movement (%active) and ABs per hour were calculated based on the entire duration of the recording (Fig. 1).

Predictive modeling and statistical analysis

As the dataset includes multiple observations (both legs) per patient and exhibits linearity as evaluated by exploratory data analysis, a generalized linear mixed model (GLMM) to account for intra-patient correlation by using individual patients as a random effect was chosen. Given the numerous independent variables of interest, including demographic, clinical, and activity-related features, a rigorous approach to model selection and validation to prevent overfitting was required. Therefore, we employed regularization with Least Absolute Shrinkage and Selection Operator (LASSO), which penalizes the GLMM model via L1-norm and in effect shrinks the weight of non-contributing features to zero.

First, multicollinearity among predictors was mitigated by excluding variables with a variance inflation factor (VIF) exceeding 5 (removing AB per hour and SOFA) [21]. Next, standardization (z-score normalization) of the remaining prediction variables (age, sex, baseline RFM muscle mass, mSOFA, calorie deficit, protein deficit, overall intensity, %active, AB-intensity$_{log\text{-}mean}$, AB-duration$_{log\text{-}mean}$, AB-intensity$_{log\text{-}SD}$, AB-duration$_{log\text{-}SD}$) was performed to ensure equal weights and comparable units. To allow testing on unseen data, a stratified split was executed to divide the data into training (80%) and test (20%) sets. The training set was further used for optimizing the hyperparameter of GLMM-LASSO using a machine learning approach with nested cross-validation (Fig. 2) [22]. Model performance was evaluated on the test set using mean squared error, root mean squared error, mean absolute error, R-squared (squared correlation method, R2) and a plot depicting actual versus predicted values.

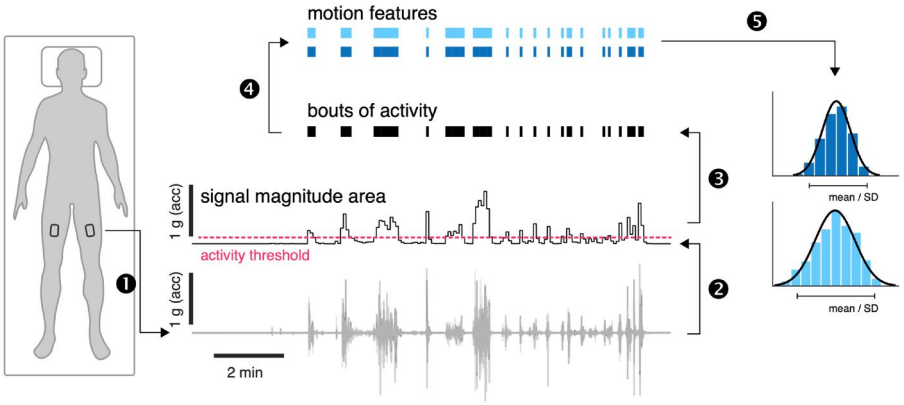

Fig. 1 Accelerometer-derived features. Body motion was monitored using tri-axial accelerometers bilaterally attached to the upper thigh (1). Raw triaxial accelerometer recordings were first offset eliminated, and the time series were segmented into non-overlapping 5 s windows. The signal magnitude area was computed for every window (2). Bouts of dynamic activity were identified based on the threshold ≥ 0.135 g (3) and a set of motion features was computed for every bout of activity (4). Finally, the average and distribution of motion features across all bouts of activity were computed (5). acc = acceleration

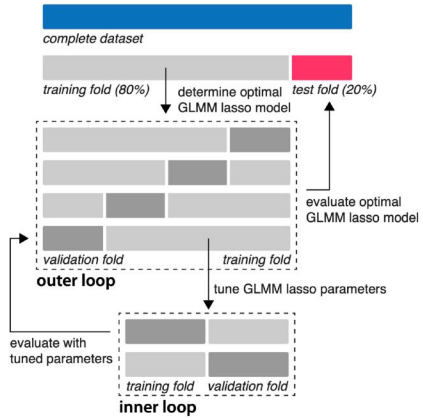

Fig. 2 Nested-cross validation of a regularized GLMM model**.** After standardization and a stratified 80/20 split, the training data set was partitioned into 4 folds (outer loop). Within each outer fold, an inner loop of 2 folds was used for hyperparameter tuning. The hyperparameter (lambda) that minimized the mean squared error in the inner loop was selected. The model with this optimal lambda was then evaluated on the validation fold of the outer loop. This process was repeated for all 4 outer folds, resulting in an optimal lambda for each fold. The final model was chosen using the average of the optimal lambdas from all outer folds. Finally, the performance of this final model was assessed using the unseen test set. GLMM = generalized mixed effects model; lasso = least absolute shrinkage and selection operator

To illustrate the level of uncertainty of the model coefficients, bootstrapping with 10,000 resamples was performed to estimate the bias-corrected and accelerated (BCa) confidence intervals for the model coefficients.

Additionally, and to test the relevance of leg movement on TM as a muscle group unaffected by thigh movement, we used a linear regression model for the prediction of TM atrophy at day 10 including all demographic, clinical and nutritional variables as well as %active as independent variables. To compare %active between healthy individuals and the neurointensive care unit (NICU) cohort, a two-tailed t-test was performed. Further, we identified patients with unilateral upper motor neuron damage and corresponding motor deficits to investigate the contribution of upper motor neuron lesion on muscle atrophy. To compare the magnitude of muscle atrophy and to account for within-subject correlation, we used Generalized Estimating Equations (GEE) with post hoc pairwise comparisons and Bonferroni adjustment.

Summary statistics for continuous variables are presented as means with standard deviation (SD) for normally distributed data and as medians with interquartile ranges (IQR) for non-normally distributed data, with normality assessed using Quantile–Quantile plots and Shapiro–Wilk test. Categorical variables are summarized as frequencies and percentages.

All analyses were performed using R (2023.06.1 + 524) using 'stats', 'psych', 'ggplot2', 'dplyr', 'lme4', 'nlme', 'geepack', 'multcomp', 'emmeans', 'MASS', 'svglite' 'glmmLasso','caret' and 'boot', packages. ChatGPT (version 4) was used for error handling, repetitive programming, and overall optimization of code in R.

Results

Patient characteristics

Out of 407 patients screened, 53 with a total of 91 available accelerometer datasets were enrolled in this study (Fig. 3). Clinical baseline characteristics are presented in Table 1. Of all patients included in the analysis, mean age was 59.2 years (SD 15.9) and 31 (58.5%) were male. Cerebrovascular diseases were the most frequent ICU admission diagnoses (86.8%, 46/53). Mean ICU length of stay was 17.0 days (IQR 8.0), while the mean duration of mechanical ventilation was 15.6 days (SD 9.2). During the observation period, patients met 62.6% (SD 18.4) of the caloric goals and 57.9% (SD 21.6) of protein goals according to the ESPEN guidelines.

Active movement and muscle atrophy during ICU treatment

Muscular atrophy as measured with ultrasound was more pronounced in RFM compared to TM (-19.5% (SD 12.0) versus -15.3% (SD 11.1) at day 10) (Fig. 4A). Active movement of NICU patients as indicated by proportion of

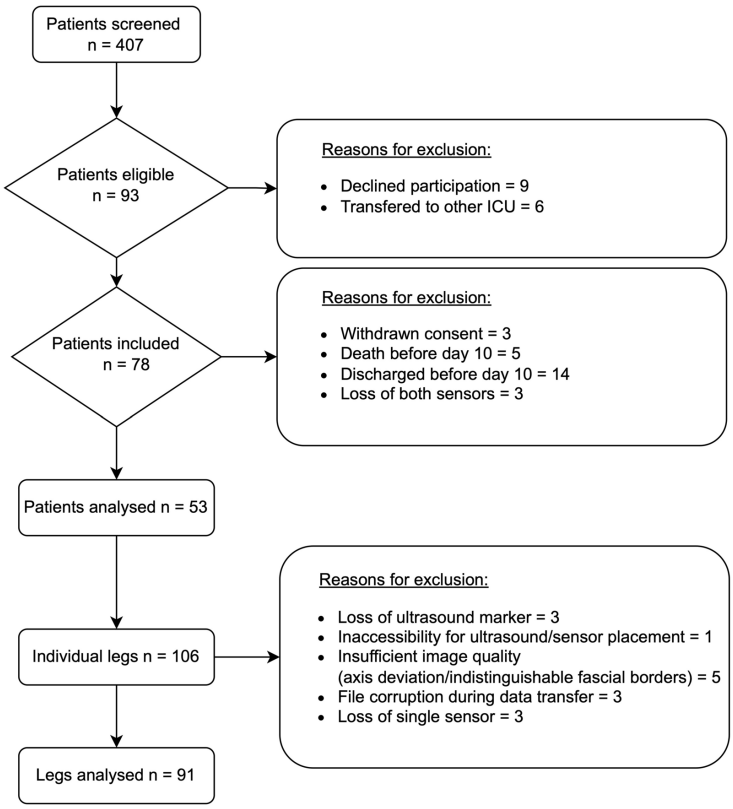

Fig. 3 Screening and study inclusion. ICU = Intensive Care Unit;

Table 1 Baseline characteristics

Parameter	n = 53
Age (years), mean (SD)	59.2 (15.9)
Male, n (%)	31 (58.5)
BMI (kg/m^2), median (IQR)	27.2 (6.2)
Baseline RFM thickness (mm), mean (SD)	10.3 (2.6)
APACHE II score at ICU admission, median (IQR)	17.0 (4.5)
SOFA score (without GCS) at ICU admission, mean (SD)	4.5 (2.1)
NUTRIC score at ICU admission, mean (SD)	3.4 (2.0)
No disability at ICU admission (pmRS = 0), n (%)	40 (75.5)
pmRS = 1, n(%)	7 (13.2)
pmRS = 2, n(%)	6 (11.3)
ICU admission diagnosis, n (%)	
Intracerebral hemorrhage	21 (39.6)
Ischemic stroke	8 (15.0)
Subarachnoid hemorrhage, non-traumatic	17 (32.1)
Meningitis/Encephalitis/other neuro-infectious disease	3 (5.7)
Status epilepticus	2 (3.8)
Guillain-Barré syndrome	1 (1.9)
Cerebral venous sinus thrombosis	1 (1.9)
Medical nutritional management	
Calories administered/calories prescribed up to day 10, % [SD]	62.6 (18.4)
Protein administered/protein prescribed up to day 10, % [SD]	57.9 (21.6)
ICU admission to sensor placement (hours), median [IQR]	42.8 (10.3)
ICU LOS, days, median (IQR)	17.0 (8.0)
Duration of mechanical ventilation, days, mean (SD)	15.6 (9.1)
Hospital LOS, days, median (IQR)	21.0 (15.0)
ICU mortality, n (%)	5 (9.6)
GOSE at hospital discharge, median (IQR)	4 (3–5)

IQR = inter-quartile range; SD = standard deviation; ICU = intensive care unit; BMI = Body Mass Index; RFM = rectus femoris muscle; APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential organ failure assessment; NUTRIC = Nutrition Risk in Critically ill score; pmRS = premorbid modified Rankin Scale; LOS = length of stay; GOSE = Glasgow Outcome Scale—Extended

active movement (%active) over time is infrequent, particular at early stages of the ICU stay. While mean %active stays low over the entire time, some patients exhibit higher activity starting around day 3. (Fig. 4B). Compared to healthy individuals, NICU patients demonstrate a significant reduction in active movement (%active: healthy individuals 13.3 (SD 0.8) vs. NICU patients 0.84 (SD 1.08), $p < 0.001$) (Supplementary Tables 2 and 4). No adverse events were observed in association with the placement of accelerometers in the ICU setting (Supplementary Table 3).

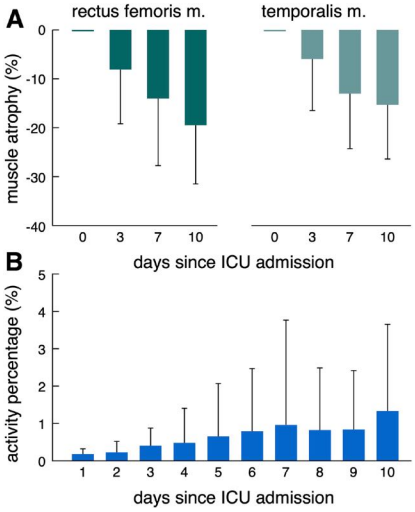

Fig. 4 Active movement and muscle atrophy during ICU treatment. Muscle atrophy at days 3, 5 7 and 10 relative to day 0 for RFM and TM (**A**). Proportion of active movement (%active) over time (**B**). ICU = Intensive Care Unit;

Predictive models for muscle atrophy

The machine learning model based on a total of 12 demographic, clinical, nutritional and accelerometer-derived variables selected baseline RFM muscle mass (beta −5.1, 95% confidence interval (95% CI) −7.9 to −3.8) and %active (beta 1.6, 95% CI 0.1 to 4.9) to explain 79% (R^2 = 79%) of the occurring variance in muscle wasting in an unseen test data set (Fig. 5, A and B). Thus, for every standard deviation increase in baseline RFM (2.6 mm), RFM thickness at day 10 is estimated to decrease by another 5.1 percentage points (49.5% relative change). In contrast, a standard unit increase in %active (1.1%) is projected to result in 1.6 percentage points less RFM atrophy at day 10 (relative change 15.5%). Ignoring movement features as predictors for RFM muscle atrophy results in substantially worse model performance (R^2 = 55%) (Fig. 5C, Supplementary Table 6). RFM atrophy was not significantly different between immobile limbs with upper motor neuron lesions (UMNL) and immobile limbs without UMNL. However, muscle atrophy was markedly decreased in limbs with active movement (Supplementary Fig. 2). Thigh-fixed accelerometer data did not contribute significantly to a model predicting TM atrophy (Supplementary Table 5).

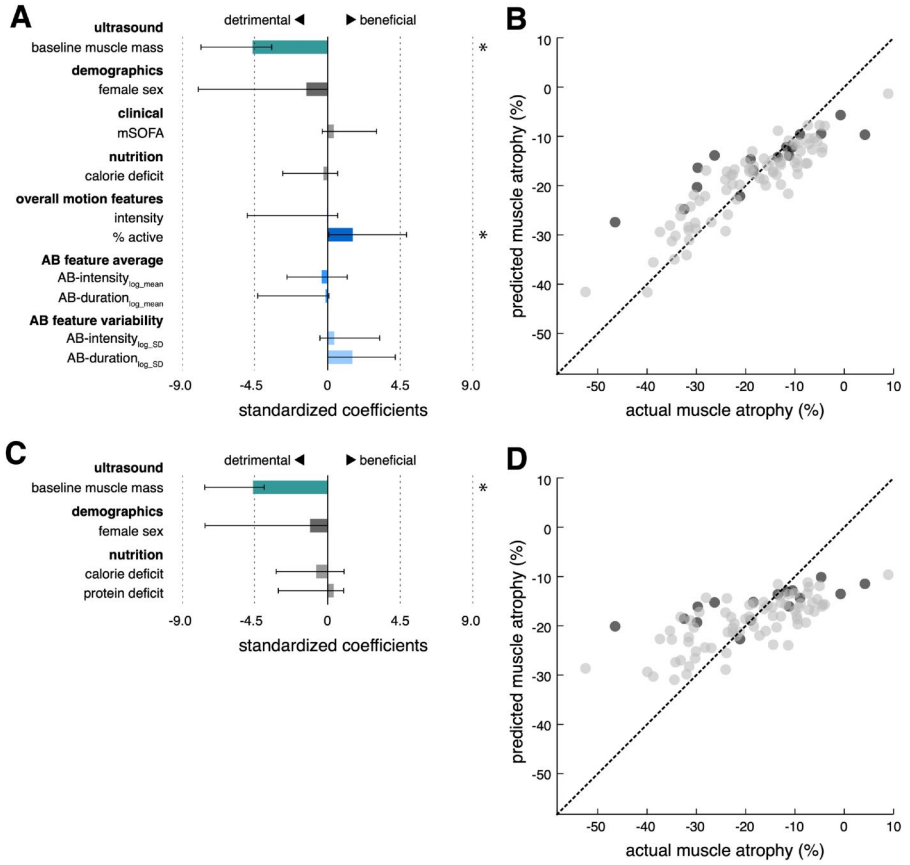

Fig. 5 Prediction of MRF muscle atrophy with and without movement features. Standardized coefficients and 95% confidence intervals (asterisks indicate significant predictors) of the regularized regression models with ($model_{movement+}$, **A**) and without movement features ($model_{movement-}$, **C**). Out of all demographic (age, sex), clinical (baseline RFM muscle mass, mSOFA), nutritional (calorie deficit, protein deficit) and movement variables (intensity, %active, AB-$intensity_{log\text{-}mean}$, AB-$duration_{log\text{-}mean}$, AB-$intensity_{log\text{-}SD}$, AB-$duration_{log\text{-}SD}$), the depicted 10/12 independent variables for model $model_{movement+}$ and 4/6 independent variables for $model_{movement-}$ were selected for the final models, respectively. Significant predictors in $model_{movement+}$ included baseline RFM muscle mass (beta − 5.1, 95% confidence interval (95% CI) − 7.9 to − 3.8) and %active (beta 1.6, 95% CI 0.1 to 4.9). For $model_{movement-}$, only baseline RFM muscle was found as a statistically significant predictor (beta − 4.6, 95% CI − 7.6 to − 3.9). Scatter plots with regression line of predicted versus actual muscle wasting (grey dots: training data; black dots: unseen test data) for $model_{movement+}$ (**B**) and $model_{movement-}$ (**D**), respectively (R^2: 0.79 vs. 0.55, RMSE: vs. 8.4 vs. 10.7 mm; MAE: 6.2 vs. 8.0 mm). mSOFA = SOFA without GCS;

Discussion

In this prospective cohort study, we used thigh-fixed accelerometers to establish movement features as predictive biomarkers for muscle atrophy in neurocritical care patients. Proportion of active movement (%active) demonstrated a significant protective effect against muscle wasting and improved the precision of muscle atrophy prediction in an unseen test data set. To the best of our knowledge, this is the first quantifiable and validated measure that provides information on the relative

importance of inactivity for muscle atrophy in critically ill patients.

It is crucial to distinguish between immobility and inactivity, especially within the ICU context, as inactivity can occur despite mobilization efforts due to a lack of active patient participation (passive movement). To address this, we excluded periods such as physiotherapy, intrahospital transports, and patient positioning, from our analysis. Therefore, we consider the movement features as surrogates for activity rather than measures of mobility. Importantly, and as a limitation of this approach, movement sensors are unable to capture any muscle activity without movement via isometric contractions (active immobility).

The relevance of inactivity, as compared to immobility, as the variable of interest in this context is further exemplified by clinical trials on electrical muscle stimulation (EMS) and interventions focusing on early (passive) mobilization. The current evidence highlights the efficacy of EMS [23, 24], whereas mobilization trials demonstrated limited efficacy and raised safety concerns [25–31]. While the latter often involve passive mobilization without genuine patient activity, EMS generates muscle activity without requiring mobility. Considering the data, a reasonable strategy to prevent muscle atrophy in critically ill patients may involve first measuring the extent of active movement with accelerometers to identify those at risk, and subsequently promoting activity (with or without mobilization) based on the patient's stability.

The pathophysiology of mechanical unloading leading to atrophy has so far only been systematically studied and quantified outside the ICU. Studies with cast immobilization of the lower extremity for two weeks in healthy adults and examination of astronauts after 8 days of space flight revealed a 5% and 6% decrease in quadriceps muscle mass, respectively [32, 33]. A recent meta-analysis analyzing the general ICU population estimated muscle atrophy to be around 16% at day 10 for RFM [34]. In comparison, our data demonstrate a more pronounced rate of RFM atrophy, showing a 19.5% decrease by day 10. While additional factors such as CIP, CIM, and CIPNM certainly contribute to the higher rate of atrophy in ICU patients, the residual activity in cast immobilization (via isometric contractions) and during space flight (via active movement with reduced muscle activity) may also account for the observed differences.

Given that no or passive movement was described in more than 70% of patients in the first 48 h, and still more than 40% after two weeks, in the TEAM trial [26], it is plausible to assume that inactivity also significantly contributes to ICUAW in the general ICU population. Yet, as disorders of consciousness and focal-neurological deficits are major barriers to mobilization and activity [26], this might be even more relevant for neurointensive care patients. Although our accelerometer data are not directly comparable to the ICU mobility scale used in the TEAM trial, it indicates extremely infrequent periods of active movement for most patients over a 10-day observation period, reaching only 6% (0.84/13.3) of the activity level of healthy individuals. These numbers are parallelled by data from González-Seguel et al., who found mechanically ventilated patients to be inactive during the ICU stay in over 96% of the time [35]. This, coupled with the prominence of movement features as predictors of muscle atrophy in our prospective cohort, further strengthens the significance of inactivity in (neuro-) critical care. Other studies within the ICU have investigated accelerometry primarily in the context of sleep, circadian rhythm, and sedation levels. However, these studies exhibit limitations, such as narrow observation periods and the absence of well-defined thresholds for activity measurement [36–39].

Accelerometer-derived data have also been validated as biomarkers for muscle atrophy outside the ICU setting. In a study with almost 500 elderly participants, Sanchez-Sanchez et al. investigated the association of physical activity as measured with hip-worn accelerometers and sarcopenia. Here, higher physical activity correlated with better performance in sarcopenia-related scores [40]. Similarly, Foong et al. showed a positive association of accelerometer-derived physical activity with muscle mass and muscle strength [41].

The exercise stimulus, as the ultimate determinant for activity, can be delineated into two primary variables: volume and intensity. In exercise physiology, the volume of exercise is traditionally quantified by the number of repetitions performed, while intensity is commonly measured by the force exerted during exercise [42]. In our ICU cohort, we utilized proportion of active movement (%active) and AB-duration$_{\text{log-mean}}$ as proxies for exercise volume. For critically ill patients, the force generated cannot be measured pragmatically. We therefore introduced movement intensity (resultant acceleration magnitude) as a surrogate of exercise intensity. The LASSO regularization used to address the high number and potential co-linearity of parameters revealed %active as an approximation of exercise volume as a relevant predictor, while surrogates of intensity were not selected. Thus, intensity may either be irrelevant considering the uniform force generated by patients moving against gravity and not against resistance, or movement intensity is not a valid biomarker of the exercise intensity.

Besides proportion of active movement, baseline muscle mass was predictive of muscle atrophy. This finding is in line with studies in healthy participants. Here, higher age with lower baseline muscle mass showed significantly

less pronounced atrophy. However, older participants with lower baseline muscle mass suffered from greater loss of muscle strength after immobilization [43–45]. Furthermore, variations in atrophy can be observed across muscle and fiber types. Anti-gravity muscles with high proportions of slow type 1 fibers, such as RFM, seem to exhibit a selective vulnerability [45], which is in line with our data demonstrating pronounced atrophy of RFM over TM.

The strengths of our study include the selection of a neurointensive care population devoid of frailty, specifically targeting individuals at high risk of muscle atrophy without pre-existing muscle wasting. However, the study's focus on neurocritical care may limit its generalizability and further research is needed to confirm the applicability of our results to more diverse patient populations. The extent of neurogenic atrophy mediated via various damage to the lower motor neuron was not explicitly measured in our study but can be assumed to be minimal given the demographics of our cohort. As that general ICU cohorts also experience lower motor neuron lesions due to critical illness or its treatments, this confounder is likely to be similar across groups. For UMNL, we do not expect neurogenic atrophy, as it does not result in direct muscle denervation. Supporting this pathophysiological hypothesis, we could not observe any difference in the extent of muscle atrophy between immobile limbs with upper motor neuron lesions (UMNL) and immobile limbs without UMNL. However, muscle atrophy was markedly decreased in limbs with active movement, suggesting no role for UMNL as a mediator for atrophy. We ensured high data quality by filtering out passive mobilization and prospectively collecting clinical data. Furthermore, our analysis is underpinned by a strong statistical framework leveraging machine learning to identify the most important predictors and using unseen data to validate these findings. Further limitations of our study are primarily rooted in the fact that muscle morphology does not necessarily equate to function. We used muscle ultrasound, a widely adopted and validated surrogate for ICUAW [34, 46, 47], instead of the Medical Research Council Sum Score (MRC-SS), as the latter is often deemed infeasible in the general ICU cohort, and even more so in neurocritical care. Additionally, we decided against including measures of the upper extremities because muscle volume is challenging to determine via ultrasound due to variability in muscle thickness relative to positioning, difficult anatomical landmarks, and less pronounced atrophy compared to the lower extremities. Instead, we focused on the RFM as the established sonographic gold standard, along with the TM as a muscle group unrelated to the movement captured by the accelerometers.

Conclusion

Active movement, as a surrogate of muscle activity, can be quantified using non-invasive, thigh-fixed accelerometers and adds value for the prediction of muscle atrophy in neurocritical care patients. Establishing movement-derived biomarkers enables better phenotyping of ICUAW, thereby providing a foundation for tailored interventions and should be included as covariates in trials on ICUAW in the future. Studies addressing the external validity of these findings beyond the neurointensive care unit are warranted.

Abbreviations

AB	Activity bout
APACHE II	Acute physiology and chronic health evaluation II
BCa	Bias-corrected and accelerated
BMI	Body mass index
CI	Confidence interval
CIM	Critical illness myopathy
CIP	Critical illness polyneuropathy
CIPNM	Critical illness polyneuromyopathy
EE	Energy expenditure
EMS	Electrical muscle stimulation
ESPEN	European Society of Parenteral and Enteral Nutrition
GCS	Glasgow Coma Scale
GEE	Generalized Estimating Equations
GLMM	Generalized linear mixed model
GOSE	Glasgow Outcome Scale—Extended
HLF	High/low pass filter
ICU	Intensive care unit
ICUAW	Intensive care unit acquired weakness
LASSO	Least Absolute Shrinkage and Selection Operator
LOS	Length of stay
MINCE	Metabolism and nutrition in neurointensive care
MRC-SS	Medical Research Council Sum Score
mSOFA	Modified SOFA
NCS	Nerve conduction studies
NICU	Neurointensive care unit
NUTRIC	Nutrition risk in the critically ill
PICS	Post intensive care syndrome
pmRS	Premorbid modified Rankin scale
QQ	Quantile–Quantile
RFM	Rectus femoris muscle
SMA	Signal magnitude area
SOFA	Sequential organ failure assessment
TM	Temporalis muscle
UMNL	Upper motor neuron lesion

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05067-y.

Supplementary Figure 1. Accelerometer placement. Figure 2. Influence of movement and upper motor neuron lesion on muscle atrophy. Table 1. Reliability of RFM ultrasound measurements. Table 2. Negative and positive controls. Table 3. Adverse events of accelerometer placement. Table 4. Accelerometer data. Table 5. Linear regression model for TM atrophy. Table 6. Performance metrics of models with and without movement features.

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Author contributions
Conceptualization, methodology, validation: MLS, MW, KD. Data curation, formal analysis, visualization, software: MLS, MW. Investigation: TP, LG, LR, AM. Writing—original draft: MLS, TP, MW. Writing—review and editing: LG, LR, AM, JZ, TW, KD. Resources: MW, TW, KD. Project administration, supervision, funding acquisition: MLS, KD. All authors reviewed the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Matlab code for analyzing motion features is available at https://github.com/DSGZ-MotionLab/ICU_motion_analysis/.

Declarations

Ethics approval and consent to participate
Approval for this study was granted by the local ethics committee (LMU Munich, approval number: 22-0173, data of approval: 11.04.2022). This study was conducted in accordance with the Declaration of Helsinki and ethical guidelines for medical and health research involving human subjects. Written informed consent was obtained from all patients or next of kin.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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5. Originalarbeit II

Mein Beitrag zu dieser Publikation bestand in erster Linie in der Patientenrekrutierung, der Durchführung aller relevanten Messungen und der Pflege und Verbesserung der Datenbank. Darüber hinaus führte ich die Datenerhebung des 3-Monate Follow-ups durch und korrigiert und verbesserte das initiale Manuskript.

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MDPI

Article

Diagnostic Utility of Temporal Muscle Thickness as a Monitoring Tool for Muscle Wasting in Neurocritical Care

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Abstract: Temporalis muscle (TM) atrophy has emerged as a potential biomarker for muscle wasting. However, its diagnostic utility as a monitoring tool in intensive care remains uncertain. Hence, the objective of this study was to evaluate the diagnostic value of sequential ultrasound- and computed tomography (CT)-based measurements of TM thickness (TMT). With a prospective observational design, we included 40 patients without preexisting sarcopenia admitted to a neurointensive care unit. TMT measurements, performed upon admission and serially every 3–4 days, were correlated with rectus femoris muscle thickness (RFT) ultrasound measurements. Interrater reliability was assessed by Bland Altmann plots and intraclass correlation coefficient (ICC). Analysis of variance was performed in subgroups to evaluate differences in the standard error of measurement (SEM). RFT decline was paralleled by ultrasound- as well as CT-based TMT measurements (TMT to RFT: r = 0.746, $p < 0.001$; CT-based TMT to ultrasound-based RFT: r = 0.609, $p < 0.001$). ICC was 0.80 [95% CI 0.74, 0.84] for ultrasound-based assessment and 0.90 [95% CI 0.88, 0.92] for CT-based TMT measurements. Analysis of variance for BMI, Heckmatt score, fluid balance, and agitation showed no evidence of measurement errors in these subgroups. This study demonstrates the clinical feasibility and utility of ultrasound- and CT-based TMT measurements for the assessment of muscle wasting.

Keywords: critical care; ultrasonography; temporal muscle; quadriceps muscle; muscular atrophy; sarcopenia

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1. Introduction

Intensive care unit acquired weakness (ICU-AW), describing the neuromuscular dysfunction secondary to critical illness, is estimated to have an incidence of around 40% in patients receiving critical care [1,2]. The main contributors seem to be sepsis, multi-organ failure, underfeeding, and lack of mobilization [3]. Besides, the paucity of suitable biomarkers hinders the monitoring of disease and thereby complicates the assessment of therapeutic approaches with regard to clinical efficacy [4].

Methods for diagnosing ICU-AW include functional testing (e.g., Medical Research Council Scale (MRC) sum score, body mass index adjusted handgrip strength, walking speed), imaging studies, electrophysiology, and biopsy. However, most tests have their limitations in critically ill and sedated patients. In neurointensive care patients, higher amounts of sedatives and the high prevalence of co-existing neurological deficits make the assessment particularly challenging.

Therefore, a lot of attention is being paid to bedside methods such as ultrasound (US) as well as to strategies to extract information on muscle wasting (sarcopenia) from imaging performed in clinical routine to minimize potential hazards associated with the assessment

for ICU-AW [5]. In a recent review on peripheral muscle ultrasound in the ICU, the authors depicted the importance of monitoring muscle wasting during the course of intensive care unit stays to assess and counteract the development of ICU-AW [6]. As a result, most ultrasound studies use rectus femoris thickness (RFT) to determine muscular atrophy as a surrogate marker of evolving sarcopenia and consequently ICU-AW [6]. As previously demonstrated, ICU-AW per se is also highly relevant to a number of ICU-related outcomes [7]. Feasible and accurate diagnostic tools are therefore necessary to monitor the development of ICU-AW. Recently, researchers have also started using measurements of temporalis muscle thickness (TMT) as a biomarker in non-ICU patients as an outcome predictor [8,9]. Estimation of temporalis muscle volume has been used as a sequential parameter for muscle wasting and was shown to correlate to early nutritional inadequacy in SAH patients in a retrospective study [10]. So far, only two studies used serial ultrasound measurements to determine changes in TMT. Hasegawa et al. introduced longitudinal temporal muscle ultrasound measurements in bedridden elderly individuals, whereas Anand et al. assessed its use in sepsis patients [11,12]. Hasegawa and colleagues could demonstrate that temporal muscle thickness decline correlated significantly with inadequate energy intake in bedridden older adults [11]. In contrast, Anand et al. questioned the usefulness of temporalis muscle as a monitoring tool for muscle wasting in sepsis patients [12].

It thus remains unclear whether TMT is of diagnostic utility to assess muscle wasting, nutrition status, and the development of ICU-AW of patients admitted to an intensive care unit in a longitudinal fashion, more so in neurocritical care patients. As sequential magnetic resonance imaging (MRI) is not feasible in critically ill patients, there is also a clinical need to determine the optimal diagnostic modality for TMT measurements.

The aim of this study was first to evaluate the utility of TMT compared to RFT in monitoring muscle wasting during the stay in a neurointensive care unit (NICU). Second, to investigate potential confounders influencing the precision of measurements in neurocritical care patients, and third, to compare US and CT-based measurements in their interrater reliability.

2. Materials and Methods

2.1. Screening and Eligibility

For this single-center prospective observational study, all consecutive patients admitted to the neurological intensive care unit were included if the age was above 18, the reason for ICU admission was of neurologic etiology, and if the expected length of stay was more than 7 days. Exclusion criteria were bifrontal craniectomy, confinement to bed prior to ICU admission, recent hospitalization, renal replacement therapy, other primary neuromuscular disease, disseminated cancer, and pregnancy. The protocol was approved by the local ethics committee of the Ludwig Maximilian University of Munich (Nr. 20-0644) for recruitment between April 2021 to April 2022.

Baseline data collected within 24 h after admission and over the course of ICU stay included age, sex, admission diagnosis, length of stay in ICU, days under mechanical ventilation, weight, height, body mass index (BMI), Glasgow Coma Scale Score (GCS), Confusion Assessment Method (CAM)-ICU-7 delirium severity scale, Richmond Agitation–Sedation Scale (RASS), Sepsis-Related Organ Failure Assessment score (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II) score and Nutrition Risk in Critically ill score (NUTRIC). Ultrasound, weighing, and laboratory tests (24 h-urine and blood parameters) were repeatedly conducted on days 3, 7, 10, 14, 17, and day 20 (or prior to discharge from ICU). For feasibility reasons, time spans of 12 h in either direction upon exact measurement day were accepted for image acquisition. The patient's weight was obtained using a Radwag C315 weighing system. Body weight estimation was conducted as described by Freitag et al. [13] and nitrogen balance was calculated as published by Kim et al. [14].

2.2. Clinical Management

Patients received caloric and protein prescriptions according to the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines [15]. General targets were

25 kcal/kg/day and 1.5 g/kg/day according to the obtained bodyweight, which was adjusted after every bodyweight estimation in 3-to-4-day intervals. Values for mean achieved calories and mean achieved protein were calculated between measurement days.

2.3. Imaging Protocols

Esaote MyLabOmega with a 20 MHz linear probe was used to obtain images. Image acquisition of subcutaneous adipose tissue (SAT), rectus femoris thickness (RFT), rectus femoris cross-sectional area (RF CSA), and vastus intermedius thickness (VIT) was performed following the protocol provided by Galindo et al. on both lower extremities [16]. As suggested by Pardo et al., the probe was placed in the lower third of the connecting line between the anterior superior iliac spine and the upper border of the patella [17]. To ensure the same measurement location over the length of stay, we drew a line on the patient's leg for probe placing. Device settings were kept identical for every patient and throughout the study period. In contrast to Chang et al., who moved the transducer cranially and parallel to the zygomatic arch until the temporal muscle was visible, we performed TMT measurements by placing the transducer on a fictive line between the zygomatic process of the frontal bone and the ipsilateral helix of the auricle (Figure 1), since this point can be identified more clearly in follow-up ultrasound acquisition processes and is furthermore comparable to the measurement point of TMT in CT [18,19]. TMT was defined as the distance between the temporal fascia and the lowest point of the temporal fossa (Figure 1). The transducer was placed rectangular to the skin with minimal pressure and bilateral measurements were performed if applicable. To reduce measurement interference, we instructed patients not to clench if not under sedation. To determine interrater reliability in ultrasound-based measurements, 20 patients were measured in parallel by two experienced examiners. The two observers were unaware of each other's results and performed measurements independently.

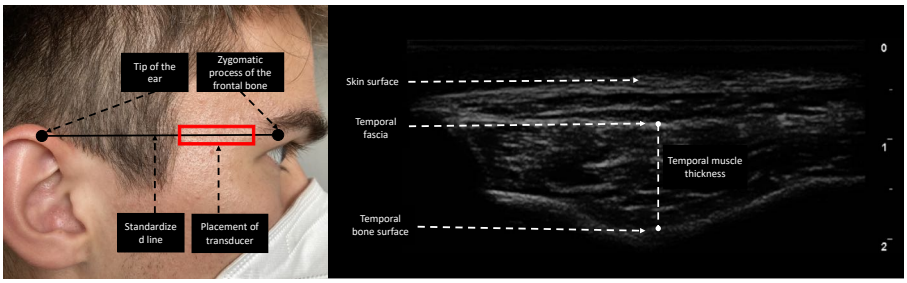

Figure 1. Measurement site of the temporal region. The reference line is the horizontal line connecting the zygomatic process of the frontal bone and the upper edge of the auricula. The transducer was placed rectangular to the skin. TMT was evaluated as the maximal distance between the temporal fascia and temporal bone surface.

Image review of CT scans was performed on a picture archiving and communication system (PACS) workstation. Determination of TMT on CT images was conducted as described by Katsuki et al. [19]. To assess interrater reliability for CT-based TMT measurements in all included patients, two observers performed these measurements independently and were unaware of each other's results. Additionally, the observers for CT-based TMT measurements were not involved in the ultrasound measurement processes.

2.4. Sample Size and Statistical Analysis

After analyzing statistical power for the correlation of ultrasound-based TMT to RFT measurements in a cohort of 10 patients, the data indicated that at least 20 patients would

be required for an α level of 0.05 and a β level of 0.20 (meaning a power of 0.80) with a correlation coefficient of $r > 0.6$. Since the assumptions of the sample size planning were based on limited pre-existing data on TMT, we decided to include 40 patients. For statistical analysis, the statistical computing language R version 4.0.4 including its packages ggplot2 and icc were used [20]. Variables are presented as frequencies with percentages, mean and standard deviation (SD) or as median and 25%/75% quartile. The relative changes of muscle diameter (Δd) at timepoint t (t) were calculated using the formula: $\Delta d_t = (d_t - d_0)/d_0$. In general, a two-sided p value ≤ 0.05 was considered statistically significant. To assess muscular atrophy, a Wilcoxon signed-rank test for paired samples referencing day 0 was used. Since the data do not suggest non-linear dependencies, the relationship among measured variables was investigated using Pearson correlation. As a significance test for correlation, Fisher's Z transform was used. To account for potential hemiparesis in NICU patients, correlations were calculated for each side. Evaluation of inter-rater reliability (IRR) was determined by Bland Altmann plots and intraclass correlation coefficient (ICC) with the according to 95% confidence intervals (CI). For ICC, the following values were used to indicate levels of reliability: <0.50, poor reliability; 0.50–0.75, moderate reliability; 0.75–0.90, good reliability; >0.90, excellent reliability [21]. Analysis of variance for the standard error of measurement (SEM) was performed using BMI, RASS, Heckmatt score, and fluid retention normalized to body weight as group-defining variables [22]. After the first visualization of the SEM for TMT measurements for all included patients on day 10, clear outliers were excluded from dichotomization. As seen for the correlation test, observations were separated for each side to minimize the influence of hemiparesis. The dichotomization of the study cohort was then performed in the four groups defining variables mentioned above to analyze the effects of possible confounders on the SEM. The following aspects were considered: (i) analysis of effects of body weight with cut-off values for group one with a BMI < 30 versus group 2 with BMI values of 30 or above (ii) analysis of the muscle echogenicity influence on SEM with cut off values for Heckmatt score < 3 for group 1 versus 3–4 for group 2 (iii) analysis of effects of agitation with dichotomization for RASS < 0 versus RASS 0–4 (iv) analysis of the implication of fluid balance. Here, dichotomization of patients was performed according to fluid retention in the first ten days of intensive care stay, with group one having a fluid retention of less than 7.5% per kilogram bodyweight versus group 2 with more than 7.5% per kilogram body weight. To test statistical differences in the SEM between the subgroups, we used the F-test.

3. Results

3.1. Study Demographics and Nutritional Characteristics

Baseline data are summarized in Table 1. Overall, 40 patients were enrolled with a minimum ICU follow-up of 10 days. Twenty-six study participants stayed until measurement day 14, 21 until day 17 and 12 patients were monitored up to day 20. The median age was 60 years (IQR 52.75–73.5) and most patients were male (31/40). On admission, the mean BMI was 29.3 (SD 4.3) and the most frequent cause for ICU admission was cerebrovascular disease (32/40). The median length of ICU stay (LOS) was 20 days (IQR 13–34), with a median time of mechanical ventilation of 11.5 days (IQR 8.5–22.25). From day 1 to day 10, patients received a mean of 983.05 kcal/day (SD 310.12 kcal/day). A mean protein intake of 0.66 g/kg/day (SD 0.42 g/kg/day) was achieved in the same time span. Nitrogen balance as a surrogate marker for protein catabolism was negative on day 10 with a mean value of −8.5 g/day (SD 7.1 g/day).

Table 1. Patient demographics and critical illness parameters.

Parameter	n = 40
Age (years), median [IQR]	60 [52.75–73.5]
Male, n (%)	31 (78%)
BMI (kg/m^2), mean (SD)	29.3 (4.3)
APACHE II score at ICU admission, median [IQR]	12 [9–18]
NUTRIC score at ICU admission, median [IQR]	3 [2–5]
pMRS = 0 upon admission, n (%)	34 (85%)
Heckmatt score upon admission, median [IQR]	2 [2–3]
ICU admission diagnosis, n (%)	
Intracerebral hemorrhage	12 (20%)
Ischemic stroke	10 (25%)
Subarachnoid hemorrhage	9 (22.5%)
Meningitis/Encephalitis/other neuro-infectious disease	6 (15%)
Status epilepticus	2 (5%)
Cerebral venous sinus thrombosis	1 (2.5%)
Time to baseline ultrasound measurement, days, mean (SD)	0.98 (0.77)
ICU LOS, days, median [IQR]	20 [13–34]
Duration of mechanical ventilation, days, median (IQR)	11.5 [8.5–22.25]
Hospital LOS days, median [IQR]	24 [19–38]
ICU mortality, n (%)	4 (10%)
Nutritional parameters:	
Mean achieved calories from day 1 to 10 in kcal/day (SD)	983.05 (310.12)
Mean achieved protein from day 1 to 10 in g/kg/day (SD)	0.66 (0.42)
Nitrogen balance on day 10 in g/day (SD)	−8.5 (7.1)

IQR = Inter-Quartile Range; SD = Standard Deviation; ICU = Intensive Care Unit; BMI = Body Mass Index; APACHE II = Acute Physiology and Chronic Health Evaluation; NUTRIC = Nutrition Risk in Critically ill score; pMRS = premorbid Modified Rankin Scale; LOS = Length of Stay.

3.2. Muscular Atrophy Characteristics

In multimodal measurements of TMT (CT and US) and in the ultrasound-based measurement of RFT, a substantial decline in muscle mass was detected during the ICU stay as presented in Figure 2. In ultrasound-based measurements, TMT declined from 10.9 mm (SD 1.6 mm) at baseline to 10.1 mm (SD 1.4 mm) on day 10 and 9.6 mm (SD 1.3 mm) on day 20, whereas RFT declined from 10.1 mm (SD 2.6 mm) at baseline to 8.5 mm (SD 1.9 mm) and 7.6 mm (SD 1.4 mm) at day 10 and day 20, respectively. TMT measured in serial CT scans declined from 9.0 mm (SD 2.2 mm) at baseline to 7.6 mm (SD 1.2 mm) on day 10 and 6.3 mm (SD 0.7 mm) on day 20.

3.3. Inter-Rater Agreement

Figure 3 shows the Bland–Altmann plots of TMT measurements visualizing inter-rater agreement between examiner 1 (E1) and examiner 2 (E2). The mean bias was −0.189 mm, and the upper limit of agreement (LOA) was 1.55 mm, while a lower LOA of −1.93 mm was acknowledged in ultrasound-based TMT measurements. As for ICC in ultrasound-based measurements, we observed a value of 0.797 (95% CI 0.737, 0.844). Furthermore, we analyzed 156 CT images of 39 patients retrospectively with two blinded observers, where the mean bias was −0.005 mm with an upper LOA of 2.03 mm and a lower LOA of −2.04 mm. Moreover, the ICC of E1 and E2 showed overall good agreement with a value of 0.899 (95% CI 0.88, 0.92).

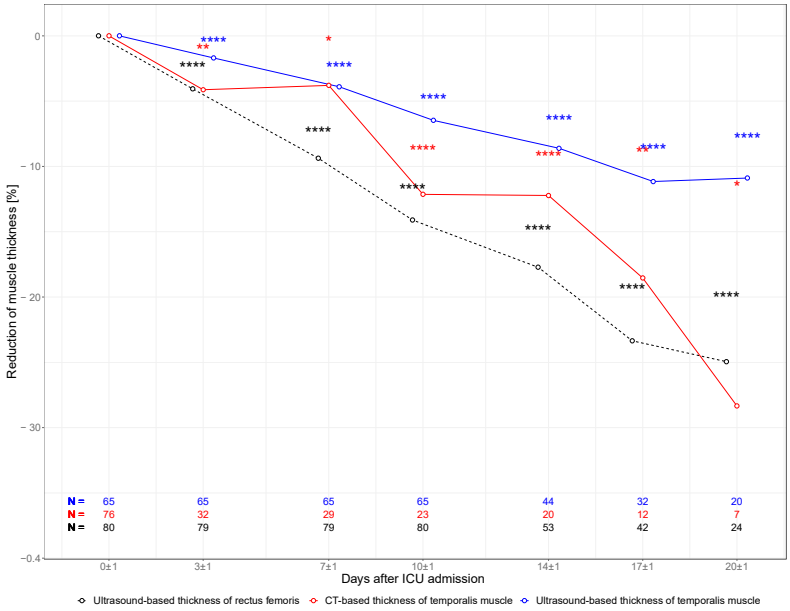

Figure 2. Muscle characteristics. Change in TMT and RFT within the first 20 days of ICU stay. Percent change of muscle thickness in ultrasound-based measurements of TMT (blue line), CT-based TMT (red line), and ultrasound-based RFT (black dotted line). Each measured muscle was treated as a unit of analysis. Correspondingly, n equals double the number of patients included in the study. * $p < 0.05$; ** $p < 0.01$; **** $p > 0.0001$ (p values for the Wilcoxon signed-rank test for paired samples referencing day 0).

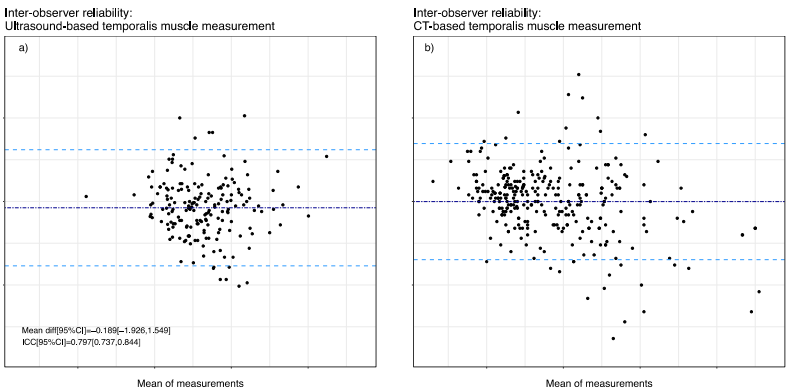

Figure 3. Inter-observer reliability between the two measurement techniques. Bland Altman representation with mean differences (dark blue dashed line) and 1.96 SD limits (light blue dashed lines). (**a**) Inter-observer reliability of ultrasound-based TMT measurements. (**b**) Inter-observer reliability of CT-based TMT measurements.

3.4. Correlation of TMT Muscle Loss between Ultrasound and CT Measurement

Ultrasound-based RFT and ultrasound-based TMT (left side r = 0.746, $p < 0.001$; right side r = 0.631, $p < 0.001$) as well as ultrasound-based RFT and CT-based TMT measurements (left side r = 0.609, $p < 0.001$; right side r = 0.592, $p < 0.001$) showed significant correlation. (Figure 4).

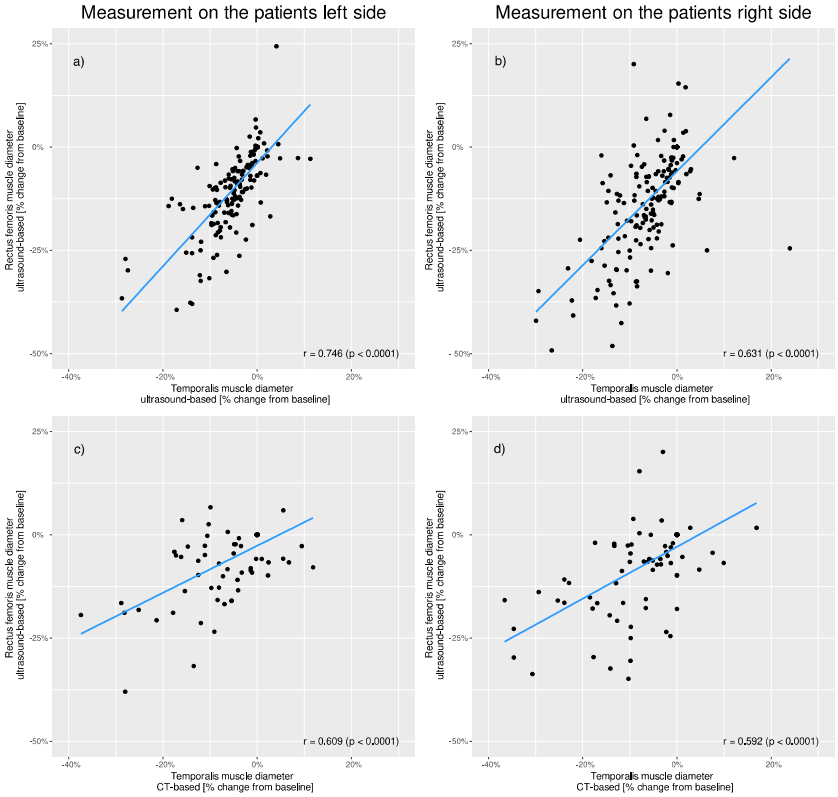

Figure 4. Correlation of percentage changes in muscle thickness between different muscle groups and different measurement techniques. Comparison of the patients' (**a**) left and (**b**) right-sided ultrasound-based rectus measurements to ultrasound-based temporalis measurements. Comparison of the patients' (**c**) left and (**d**) right-sided ultrasound-based rectus measurements to CT-based temporalis measurements.

3.5. Analysis of Variance for Possible Confounders

BMI, Heckmatt score, RASS, and fluid retention did not significantly influence the standard error of measurement in our analysis. Graphic visualization of the different aspects can be seen in Figure 5.

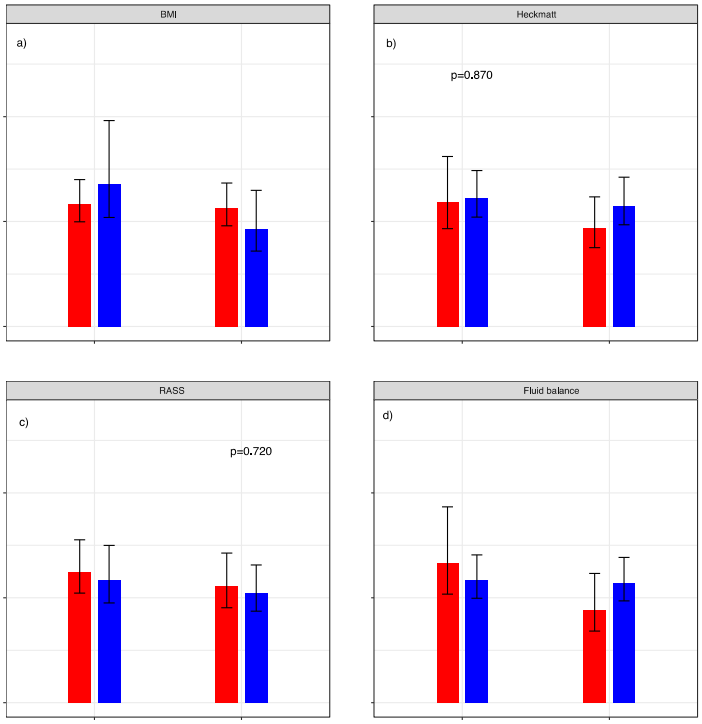

Figure 5. Standard error of measurement relative to patient characteristics. SEM with dichotomization of (**a**) BMI: red graphs represent < 30 versus blue graphs ≥ 30. (**b**) Heckmatt score: red graphs represent cohort with values < 3 and blue graphs ≥ 3. (**c**) RASS score: red graphs represent cohort with values < 0 und blue graphs ≥ 0. (**d**) Fluid retention normalized to body weight: red graphs represent cohort with values < 7.5% (red) versus blue graphs ≥ 7.5%. *p*-values for the calculated F-test are given above the respective graphs.

4. Discussion

In this single-center observational study, ultrasound- and CT-based TMT measurements exhibited diagnostic utility to monitor muscle wasting in a cohort of neurocritical care patients as (i) TMT and RFT showed comparable results in sequential measurements and (ii) high inter-rater reliability in both CT- and ultrasound-based measurements up to 20 days was noticed and (iii) robustness to potential confounders with high prevalence in neurocritical care such as BMI, a difference of muscle echogenicity, agitation and changes in fluid balance was observed.

When establishing an imaging protocol as a diagnostic strategy to monitor muscle wasting as an important aspect of ICU-AW in neurocritical care, important key points are the selection of the most suitable muscle, the most pragmatic and accurate method of measurement, and the validity of sequential measurements with analysis of potential confounders.

Concerning the most appropriate muscle, we could demonstrate that TMT is a promising alternative to the well-established RFT. Average baseline values in studies assessing TMT via ultrasound range from 4.9 mm to 9.7 mm depending on the measuring point [18,23]. Both TMT and RFT decline in our study demonstrated a similar extent and

pattern compared to previous studies, thereby highlighting external validity for TMT measurement [10,11,24,25]. Moreover, the decline in thickness correlated significantly between both muscles.

In previous critical care trials on the topic of muscle wasting and ICU-acquired weakness, the most frequently examined sites included the tibialis anterior, rectus femoris, and vastus intermedius muscle [6]. However, RFT measurement bears some disadvantageous aspects concerning confounders and clinical relevance, especially in neurocritical care patients. First, the influence of paralysis on thickness decline is not known. Second, for repeated measurements, patient positioning requires to be completely flat, with legs in a relaxed horizontal position to reach optimal inter-rater and intra-rater reliability [17]. As rigorous positioning regimes with suboptimal leg positioning for ultrasound assessment of RFT are part of neurocritical care in patients with critical intracranial pressure, RFT seems to be less suitable.

Moreover, studies showed an earlier and more severe atrophy in muscles with type 2 fibers being dominant in thigh muscles, but underrepresented in jaw-closing muscles, especially in temporalis muscle [24,26,27]. This might partly explain the higher reduction of RFT compared to TMT in our data. Given these differences, the clinical significance of the respective muscles is of particular interest.

Regarding the most suitable method, ultrasound for TMT evaluation was used by different working groups in different methodical setups and patient cohorts. Studies with single-time measurements focused mainly on capturing sarcopenia as a prognostic marker, on the reliability of measurements, and on the influences of different postures and voluntary muscle contraction on ultrasound-guided imaging [18,23]. Similar to previous studies, the ultrasound-based measurement of TMT in our study was feasible and showed a good inter-rater reliability [18,23]. Longitudinal measurements introduced by Hasegawa et al. were carried out focusing on the correlation of energy intake inadequacy to temporal muscle atrophy in bedridden elderly non-ICU patients [11]. Only one further study intended to monitor sarcopenia in an ICU setting by performing serial ultrasound measurements of TMT in sepsis patients [12]. Here similar atrophy characteristics, but no significant correlations between RFT and TMT were acknowledged. This disagreement with our data might be explained by differences in patient selection (only patients with sepsis and not accounted for possible preexisting sarcopenia) as well as by the image acquisition processes and length of observation.

Although TMT appears to be appropriate for assessing muscle wasting and there is some evidence suggesting TMT correlates with dysphagia as well as hand grip strength and therefore possibly also with ICU-AW [28,29]. Larger prospective studies are required to answer the question of whether TMT is a suitable surrogate to evaluate dysphagia or whether it can drive weaning and nutritional strategies. However, the following points appear to make ultrasound-based TMT measurements attractive for monitoring muscular atrophy, particularly in neurocritical care. First, the measurement point is easy to identify using the anatomical landmarks described above. Second, measurements can be achieved in a 'one stop shop' approach by combining it with ultrasound examinations frequently applied in neurocritical care (optic nerve sheath diameter (ONSD), third ventricle diameter, transcranial doppler (TCD)) [30]. Third, and inherent to ultrasound techniques in general, it allows bedside, cost-effective and real-time assessment. Fourth, as no effects of possible confounders could be detected, ultrasound-based TMT measurements seem to be a reliable method.

CT- and MRI-based TMT measurements based on routine imaging scans have shown their practicality in evaluating preexisting sarcopenia and patient outcome [31]. Steindl et al. even defined standard values of TMT in MRI in the Caucasian population [29]. By using semi-automated software for CT-based TMT measurements, Onodera et al. could demonstrate the detection of developing sarcopenia in SAH patients [10]. Paralleling this work, our study presented a similar progressive TMT decline in CT-based measurements. This might be of relevance since brain imaging methods are widely used in NICU patients.

Yet, not all patients need serial CT scans and timing of imaging, with the vast majority of scans at the early phase of the disease, might hinder detailed monitoring of long-term outcomes such as sarcopenia or ICU-AW.

As shown in our study the decline pattern of TMT matches the one of RFT, and both methods (Ultrasound and routine CT scans) seem to adequately capture muscle wasting. However, the value of sequential measurements must be assessed in prospective interventional studies with different nutritional and mobilization strategies based on TMT decline in preset time points. The fusion of different imaging processes could possibly improve measurement accuracy and should be looked at in future studies.

This is the first trial that systematically evaluates the relevance of different methods and muscles with short-interval follow-up measurements in NICU patients. Due to its prospective nature, the rigorous inclusion criteria, and the monitoring of clinical, nutritional, and laboratory data, the study also allows an evaluation of relevant confounders.

This study had several limitations. As this was a single-center study investigating NICU patients with a prolonged stay in NICU, caution must be taken in generalizing the findings. Nevertheless, the atrophy of rectus femoris in our study was similar to findings in more general populations with less strict inclusion criteria, which supports the external validity argument. Moreover, based on the cut-off points of Steindl and colleagues only three recruited study patients in this study showed TMT values below two standard deviations, meaning that only 7.5% were defined as pre-sarcopenic, which coincides with the low rate of pMRS score greater than 0 in our study cohort and speaks for good internal validity. Also, as we used a slightly different angle for ultrasound-based TMT measurements, comparability with other studies is hindered. Yet, studies using volumetric methods (which are independent of the exact measuring point for TMT) seem to have similar results. Finally, the pattern of decline was in line with the one found in previous studies, which alleviates the need for a precise measurement point for single-center studies. However, to improve comparability across studies a consensus statement must be made concerning the exact measuring method and point [32]. There were some missing data for CT-based TMT due to surgery or trauma or the sheer absence of follow-up imaging.

5. Conclusions

In the perspective of the findings, temporalis muscle thickness is a promising surrogate marker for muscle wasting in critically ill neurological patients. All subjects portrayed progressive decline of TMT in ultrasound- as well as CT-based measurements, which was paralleled by muscle wasting of the rectus femoris muscle. Demonstrating good reliability in both TMT measurement techniques, and by evaluating factors potentially confounding the diagnostic accuracy, this study demonstrates the clinical feasibility and utility of temporalis muscle measurement to monitor muscle wasting in a neurocritical care setting.

Author Contributions: Conceptualization, A.M., K.D. and M.L.S.; Methodology, A.M., K.D., S.K. and M.L.S.; software, A.M. and R.R.; validation, M.L.S. and K.D.; formal analysis, R.R.; investigation, A.M., S.K., S.R., V.I. and T.P.; data curation, A.M., S.K., S.R., V.I. and T.P.; writing—original draft preparation, A.M.; writing—review and editing, A.M., M.L.S. and K.D.; visualization, R.R.; supervision, K.D. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: We obtained approval for this study from the local Munich Ethics Committee where the study was conducted (approval number: 20-0644). This study was conducted in accordance with the Declaration of Helsinki and ethical guidelines for medical and health research involving human subjects.

Informed Consent Statement: Informed consent was obtained from all individual participants included in this study, or from their legally authorized representatives.

Data Availability Statement: Data supporting the findings of this study are available from the corresponding author (Konstantinos Dimitriadis) on reasonable request. The data are not publicly available due to ethical restriction.

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Conflicts of Interest: The authors declare no conflict of interest.

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