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Arzneimittel bei stationärer Aufnahme als prädiktiver Risikofaktor für postoperatives Delir

Dissertation

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Für meine Großeltern –

Danke für eure Unterstützung und Vorbildfunktion

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Arzneimittel bei stationärer Aufnahme als prädiktiver Risikofaktor für postoperatives Delir

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München, 16.09.2025

Ort, Datum

Carolin Christiane Geßele

Unterschrift Doktorandin

Inhaltsverzeichnis

I. Abkürzungsverzeichnis

ACB	Anticholinergic Burden
AUC	*Area under the curve*
COPD	Chronisch obstruktive Lungenerkrankung
DBI	*Drug Burden Index*
DevC	*Development cohort*
DRD-Score	*Risk score including delirium risk-increasing drugs*
EntK	Entwicklungskohorte
extMARANTE	*Extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure*
GABA	Gamma-Aminobuttersäure
GerACB	*German Anticholinergic Burden*
GerDBI	*German Drug Burden Index*
MARANTE	*Muscarinic Acetylcholinergic Receptor ANTagonist Exposure*
NPV	*Negative predictive value*
OSAS	Obstruktives Schlafapnoesyndrom
PPV	*Positive predictive value*
ROC	*Receiver operating characteristic*
ValC	*Validation cohort*
ValK	Validierungskohorte

Hinweis zu gendergerechter Sprache

Um die Lesbarkeit, sowie das textliche Verständnis in folgender Arbeit zu gewährleisten, wird auf die gleichzeitige Verwendung der Sprachformen männlich, weiblich und divers (m/w/d) verzichtet. Sämtliche Personenbezeichnungen gelten gleichermaßen für alle Geschlechter.

II. Publikationsliste

Veröffentlichungen als Bestandteile der kumulativen Dissertation

Veröffentlichung I: Geßele C, Rémi C, Smolka V, Dimitriadis K, Amann U, Saller T, Strobach D. Anticholinergic exposure, drug dose and postoperative delirium: Comparison of dose-related and non-dose-related anticholinergic burden scores in a retrospective cohort study of older orthopaedic and trauma surgery patients. Drugs & Aging. 2024;41(12):1003-13. https://doi.org/10.1007/s40266-024-01159-0

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Veröffentlichungen (weitere)

Morath B, Meid AD, Zaradzki M, Geßele C, Nüse S, Chiriac U, et al. Analysing and improving preoperative medication management in cardiac surgery. British Journal of Clinical Pharmacology. 2023;89(4):1349-59. https://doi.org/10.1111/bcp.15570

Vorträge

„Postoperatives Delir und Arzneimittel: Entwicklung und Anwendung eines prädiktiven Risikoscores“. 2. Gemeinsame Doktorandentagung Klinische Pharmazie, 22.-23.11.2024, Hamburg

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„Delirogene Medikamente – mehr als Priscus?“. 1. Münchner Delirtag, 15.03.2023, München

Poster

Geßele C, Saller T, Smolka V, Dimitriadis K, Amann U, Strobach D. Arzneimitteltherapiesicherheit im Alter: präoperatives Screening nach Risikopatienten für postoperatives Delir mit Einnahme von Risikoarzneimitteln. 6. Kongress für Patientensicherheit bei medikamentöser Therapie 2024, Berlin

Geßele C, Saller T, Dimitriadis K, Amann U, Strobach D. Entwicklung und Validierung eines prädiktiven Risikoscores für Arzneimittel-bedingtes postoperatives Delir an orthopädischen und unfallchirurgischen Patienten. DGKPha Jahrestagung 2023, Münster

Geßele C, Omeima T, Brüll K, Strobach D. Postoperatives Delir und anticholinerge Last: muss die Dosierung berücksichtigt werden? 8. Kongress für Arzneimittelinformation der ADKA 2023, Köln. Ausgezeichnet mit dem 1. Posterpreis

Geßele C, Saller T, Dimitriadis K, Mannell H, Strobach D. Weiterentwicklung eines prädiktiven Screening-Scores für postoperatives Delir - Pilotauswertung von Risikofaktoren und Delir-relevanten Arzneimittel bei stationärer Aufnahme orthopädischer und unfallchirurgischer Patienten. DGKPha Jahrestagung 2022, Heidelberg

Geßele C, Soethoff J, Zaradzki M, Nüse S, Chiriac U, Hoppe-Tichy T, Karck M, Morath B. Verbesserungspotential im präoperativen Medikationsmanagement herzchirurgischer Patienten – eine retrospektive Analyse. ADKA-Kongress 2022, Nürnberg

1. Beitrag der Doktorandin zu den Veröffentlichungen

1.1 Beitrag zu Veröffentlichung I

Der Studienentwurf wurde von der Doktorandin Carolin Geßele unter Beratung von Dr. Dorothea Strobach entwickelt. Die Datenerhebung erfolgte durch die Doktorandin. Das methodische Vorgehen zur Entwicklung und Validierung des Scores wurde von der Doktorandin mit Unterstützung von PD Dr. Ute Amann entwickelt. Die statistische Auswertung, die erste Interpretation und Darstellung der Ergebnisse sowie die Diskussion der Ergebnisse erfolgten durch die Doktorandin. Dr. Dorothea Strobach, PD Dr. Ute Amann, PD Dr. Thomas Saller und Prof. Konstantinos Dimitriadis standen bei der Diskussion der Ergebnisse beratend zur Seite. Der Entwurf für das Manuskript zur Veröffentlichung wurde von der Doktorandin verfasst und von Dr. Dorothea Strobach Korrektur gelesen. Alle Koautoren haben das Manuskript vor der Veröffentlichung gelesen und der Einreichung zugestimmt. Die Tabellen und Abbildungen wurden von der Doktorandin erstellt. Die Doktorandin war die korrespondierende Autorin und hat die Kommunikation mit Editoren, Reviewern und Koautoren im Rahmen des Publikations- und Review-Prozesses selbstständig durchgeführt.

1.2 Beitrag zu Veröffentlichung II

Die Planung der Studie erfolgte durch die Doktorandin Carolin Geßele mit Unterstützung von Dr. Dorothea Strobach und PD Dr. Thomas Saller. Die Datenerhebung wurde von der Doktorandin sowie teilweise von wissenschaftlichen Hilfskräften unter Anleitung der Doktorandin durchgeführt. Die Doktorandin koordinierte die Abstimmungen des Expertenpanels zur Erweiterung der MARANTE-Skala und wertete die Bewertungen im Konsensverfahren aus. Die statistische Auswertung, die erste Interpretation und Darstellung der Ergebnisse sowie die Diskussion der Ergebnisse erfolgten durch die Doktorandin. PD Dr. Ute Amann und Dr. Dorothea Strobach unterstützten bei der Diskussion der Ergebnisse. Der Entwurf des Manuskripts zur Veröffentlichung wurde von der Doktorandin verfasst und von Dr. Dorothea Strobach Korrektur gelesen. Alle Koautoren haben das Manuskript vor der Veröffentlichung gelesen und der Einreichung zugestimmt. Die Tabellen und Abbildungen wurden von der Doktorandin erstellt. Die Doktorandin war die korrespondierende Autorin und hat die Kommunikation mit Editoren, Reviewern und Koautoren im Rahmen des Publikations- und Review-Prozesses selbstständig durchgeführt.

2. Einleitung

2.1 Das postoperative Delir

Das Delir ist eine akute und fluktuierende Störung der Aufmerksamkeit, des Bewusstseins und der Kognition [1]. Abhängig vom betrachteten Patientenkollektiv variiert die Delirprävalenz von 23 % bei hospitalisierten älteren Patienten, über 11-51 % bei älteren Patienten mit operativen Eingriffen bis zu 75 % bei beatmeten Intensivpatienten [2-4]. Im ambulanten Setting ist die Prävalenz von Delir niedriger mit 1-2 % [3]. Nach operativen Eingriffen ist das postoperative Delir die häufigste Komplikation bei Patienten ≥ 65 Jahre [5].

Ein Delir ist mit negativen Folgen wie einem erhöhten Risiko für langfristige kognitive und funktionelle Beeinträchtigungen, verlängerter Hospitalisierung, erhöhter Mortalität und höheren Kosten für das Gesundheitssystem assoziiert [5]. In der psychomotorischen Ausprägung des Delirs gibt es hyperaktive und hypoaktive Formen, sowie die am häufigsten vorkommende Mischform. Hyperaktive Phasen sind deutlich ausgeprägt und durch Agitation, Stimmungsschwankungen bis hin zu psychotischen Symptomen wie Halluzinationen gekennzeichnet [6]. Hypoaktive Phasen zeichnen sich durch Müdigkeit und verminderter Aktivität aus, wodurch das Delir häufig unerkannt bleibt und mit einer ungünstigeren Prognose einhergeht [3].

Die grundlegenden pathophysiologischen Mechanismen des Delirs sind noch nicht vollständig aufgeklärt. Es gibt Hinweise auf eine Reihe von miteinander verbundenen Faktoren wie Veränderungen im Neurotransmitterhaushalt, Entzündungsparameter, physiologische Stressfaktoren und Elektrolytstörungen, die direkt oder indirekt die neuronale Aktivität beeinträchtigen [7]. Am häufigsten werden ein relativer Acetylcholinmangel, ein dopaminerger Überschuss, eine Noradrenalin- oder Glutamatfreisetzung sowie Veränderungen des Serotonin-, Histamin- oder Gamma-Aminobuttersäure (GABA)-Spiegels beschrieben [8]. Die neuronale Aktivität kann auch durch physiologische Stressfaktoren wie Hypoxie, extreme Temperatur- und Glukosewerte sowie Stoffwechsel- und Elektrolytstörungen beeinträchtigt werden [7].

Die effektivste Strategie zur Reduktion der Delirprävalenz sind nicht-pharmakologische Interventionen [9]. Dazu zählen Maßnahmen zur Umgebungs- und Reorientierung, Verringerung von nächtlichen Störungen zur Schlafförderung, Förderung der Tag-Nacht-Routine, tägliches Delir-Screening, tägliche Mobilisierung und eine normale Flüssigkeitszufuhr [6]. Auch die adäquate Behandlung von potenziellen Delirauslösern steht im Fokus: Korrektur von Stoffwechselstörungen, Behandlung von Schmerzen und frühzeitige Therapie von Infektionen. Bisher gibt es keine Evidenz für den Einsatz von Arzneimitteln zur gezielten Delirprophylaxe [10], wohingegen

die Vermeidung von Risikoarzneimitteln eine Präventionsmaßnahme darstellt [11]. Bei einem vorhandenen Delir umfasst die primäre Behandlungsstrategie, ähnlich wie bei der Prävention, die Behandlung von potenziellen Auslösern sowie Maßnahmen zur Reorientierung [6]. Eine medikamentöse Delirtherapie sollte nur bei Patienten mit schweren psychotischen Symptomen erfolgen, um eine Selbst- oder Fremdgefährdung zu vermeiden. Hierbei werden Antipsychotika (meist Risperidon, Quetiapin, Pipamperon oder Melperon, seltener Haloperidol) aufgrund ihrer antipsychotischen oder sedierenden Wirkung eingesetzt [12]. Der Einsatz von Antipsychotika ist nicht mit einer veränderten Dauer oder Schweregrad des Delirs, sowie einer reduzierten Mortalität oder Aufenthaltsdauer im Krankenhaus oder auf der Intensivstation assoziiert [13].

2.2 Risikofaktoren für ein postoperatives Delir

2.2.1 Prädisponierende und auslösende Risikofaktoren

Die Entwicklung eines Delirs ist multifaktoriell bedingt und beruht auf einem Zusammenspiel zwischen der bestehenden Prädisposition bei stationärer Aufnahme und der Exposition gegenüber auslösenden Risikofaktoren während des Krankenhausaufenthalts [5]. Eine hohe Anzahl prädisponierender Faktoren erhöht die Anfälligkeit für auslösende Risikofaktoren, sodass bereits eine geringe Exposition gegenüber Noxen zur Entwicklung eines Delirs führen können. **Tabelle 1** zeigt eine Auswahl prädisponierender und auslösender Risikofaktoren für das postoperative Delir. Eine mögliche Abgrenzung der Begriffe wurde von Ormseth et al. definiert [7]. Demnach bestehen prädisponierende Faktoren mindestens einen Monat vor Auftreten des Delirs, während auslösende Risikofaktoren in einem unmittelbaren zeitlichen Zusammenhang mit dem Delir stehen und akute oder subakute Veränderungen darstellen. Manche Faktoren können sowohl prädisponierend als auch auslösend wirken.

Tabelle 1: Auswahl an Risikofaktoren für postoperatives Delir [5-7]

Prädisponierende Risikofaktoren	**Auslösende Risikofaktoren**
Hohes Alter	Operative Faktoren
Kognitive Beeinträchtigung, Demenz	Art und Dauer des operativen Eingriffs
Multimorbidität	Systemische Erkrankungen, Organdysfunktion
Gebrechlichkeit	Infektion, Dehydratation, akute Nieren-
Hör- und Sehbeeinträchtigung	schädigung, Anämie, Schmerzen, Hypoxie
Depression	Metabolische Abweichungen
Anämie	Elektrolytstörung (Natrium, Kalium),
Chronische Nierenerkrankung	abnorme Glukosewerte

Tabelle 1: Fortsetzung

Prädisponierende Risikofaktoren	**Auslösende Risikofaktoren**
Lungenerkrankung (COPD oder OSAS)	Arzneimittel und Substanzentzug
Mangel- oder Unterernährung	Benzodiazepine, Opioide, anticholinerge
Polymedikation	Arzneimittel
Anticholinerge Arzneimittel	Alkohol-, Nikotin- und Substanzentzug
Zentral wirksame Arzneimittel	Iatrogene und umweltbedingte Faktoren
Alkohol- und Substanzabusus	Tag-Nacht-Desorientierung, Schlafentzug,
Zustand nach Delir	Immobilität, Blasenkatheter vorhanden

COPD chronisch obstruktive Lungenerkrankung, *OSAS* obstruktives Schlafapnoesyndrom

2.2.2 Delirrisiko-erhöhende Arzneimittel

Wie in **Tabelle 1** gezeigt, handelt es sich bei Arzneimitteln um sowohl prädisponierende als auch auslösende Risikofaktoren für das Delir. Arzneimittel in der Dauermedikation und die stationäre Aufnahmemedikation stellen einen prädisponierenden Risikofaktor dar und werden in dieser Arbeit als „Delirrisiko-erhöhende Arzneimittel" oder „*delirium risk-increasing drugs*" bezeichnet. Neu verabreichte Arzneimittel, beispielweise während eines stationären Aufenthalts oder operativen Eingriffs, sind auslösende Faktoren. Auch das abrupte Absetzen von Arzneimitteln mit Abhängigkeitspotential ist ein auslösender Risikofaktor. Arzneimittel, die ein Delir unmittelbar auslösen können, werden in der Literatur häufig als „delirogen" bezeichnet [14].

Ausgehend von der Pathophysiologie des Delirs sind insbesondere Arzneimittel mit Einfluss auf zentrale Neurotransmitter (Dopamin, Acetylcholin, GABA, Serotonin, Histamin und Glutamat) relevant [15, 16]. Hierunter fallen zunächst allgemein zentral wirksame Arzneimittel und Arzneimittel, die mit unerwünschten zentralen Nebenwirkungen assoziiert sind [17, 18]. Zudem kann das abrupte Absetzen einiger Arzneimittel das Neurotransmittergleichgewicht aufgrund von Entzugserscheinungen verschieben und damit ein Delir auslösen [6]. Neben einer direkten Wirkung auf zentrale Neurotransmitter sind auch indirekte Wirkungen möglich. Einige Substanzklassen wie Diuretika, selektive Serotonin-Reuptake-Inhibitoren sowie manche Antipsychotika und Antiepileptika können Elektrolytstörungen wie die Hyponatriämie hervorrufen, die wiederum ein potenzieller Delirauslöser ist [6, 19]. Delirrisiko-erhöhende Arzneimittel können auch Wirkstoffe sein, die bei Grunderkrankungen eingesetzt werden, die mit einem erhöhten Delirrisiko assoziiert sind [7]. Hier sind beispielsweise Antidementiva, Anti-Parkinsonmittel, Antidiabetika und COPD-Inhalativa zu nennen.

Der Einsatz von Delirrisiko-erhöhenden und delirogenen Arzneimitteln muss im Kontext der klinischen Gesamtsituation gesehen werden. Innerhalb der Substanzklassen gibt es zudem Unterschiede in der Delirrelevanz der einzelnen Wirkstoffe. Einige Opioide wie Pethidin oder Tramadol haben eine höheres delirogenes Potential als Tilidin oder Hydromorphon [14]. Ebenso sind für manche Antibiotika wie Fluorchinolone oder Linezolid delirogene Eigenschaften beschrieben [14]. Schmerzen und Infektionen müssen als potenzielle Delirauslöser adäquat behandelt werden. Unter Abwägung des Nutzen-Risiko-Verhältnisses kann der Einsatz von Delirrisiko-erhöhenden und delirogenen Arzneimitteln bei einer gegebenen Indikation somit gerechtfertigt sein.

2.2.3 Anticholinerge Arzneimittel

Neben allgemein Delirrisiko-erhöhenden Arzneimitteln sind weiterhin anticholinerge Arzneimittel von Bedeutung. Der Neurotransmitter Acetylcholin vermittelt als Hauptakteur des Parasympathikus vielfältige physiologische Wirkungen an nikotinergen und muskarinergen Rezeptoren [20]. In der Pathophysiologie des Delirs spielt die cholinerge Dysfunktion eine zentrale Rolle, da unter anderem über den muskarinergen Acetylcholin-Rezeptor 1 wichtige Funktionen für Kognition, Aufmerksamkeit und Gedächtnis im zentralen Nervensystem vermittelt werden [20, 21]. Langfristig ist eine reduzierte cholinerge Aktivität mit einem erhöhten Demenzrisiko und einer verminderten kognitiven Leistungsfähigkeit assoziiert, was zu einem erhöhten Delirrisiko führt [21]. Auch die Schwere und Dauer eines bestehenden Delirs kann durch verstärkte neuroinflammatorische Prozesse infolge einer verminderten cholinergen Innervation negativ beeinflusst werden [22].

Die Wirkung anticholinerger Arzneimittel kann therapeutisch erwünscht sein, wie beispielsweise bei urologischen Spasmolytika (Reduktion des Blasentonus bei einer überaktiven Blase) oder bei Butylscopolamin (spasmolytische Wirkung bei Beschwerden im Magen-Darm-Trakt). Bei vielen Arzneimitteln ist die anticholinerge Wirkung allerdings eine Nebenwirkung. Bei älteren Patienten besteht eine erhöhte Anfälligkeit für anticholinerge Nebenwirkungen aufgrund pharmakokinetischer und pharmakodynamischer Veränderungen sowie einer erhöhten Acetylcholinsensitivität aufgrund einer reduzierten Acetylcholinrezeptordichte [20, 23].

Die Gesamtheit der zentralen und peripheren anticholinergen Wirkung einer Medikation wird als anticholinerge Belastung bezeichnet. Die Bestimmung der anticholinergen Belastung anhand der angewandten Medikation ist mit *anticholinergic burden* (ACB)-Scores möglich. Die anticholinergen Wirkstoffe werden meist auf Basis von Literaturrecherchen, Expertenmeinungen, experimentellen Daten oder Serumessays der Acetylcholinesterase bewertet und einem entsprechenden Potenzwert zugeordnet [24]. Üblich sind Potenzwerte von 0 (keine), 1 (niedrig),

2 (mittel) und 3 (hoch). Die anticholinerge Gesamtbelastung der Medikation ergibt sich schließlich aus der Summe der Einzelwerte der einzelnen Wirkstoffe. Ab einem bestimmten Schwellenwert, meist einem ACB-Score ≥ 3, wird von einer hohen Gesamtbelastung ausgegangen [24]. Ein systematischer Review von Lisibach et al. identifizierte 19 ACB-Scores, die sich sowohl in den enthaltenen Wirkstoffen als auch in deren zugeordneten Potenzwerten unterschieden [24]. Dabei gab es Varianten, die sich an länderspezifischem Verordnungsverhalten orientieren, wie den *German anticholinergic burden* (GerACB)-Score [25] oder Scores mit besonderem Fokus auf kognitiver Belastung [26]. Zahlreiche Studien haben bereits den Zusammenhang zwischen der Einnahme von anticholinergen Arzneimitteln und klinischen Outcomes wie verminderter kognitiver Leistungsfähigkeit, Stürze, Delir und Mortalität untersucht, mit zum Teil widersprüchlichen Ergebnissen [24, 27-29].

Neben ACB-Scores, die die anticholinerge Potenz berücksichtigen, gibt es auch dosisbezogene Berechnungen. Ein neueres Konzept liefert hier die *Muscarinic Acetylcholinergic Receptor ANTagonist Exposure* (MARANTE)-Skala, in die neben der Potenz auch die Dosis der anticholinergen Wirkstoffe einfließt [30]. Ein weiteres Verfahren ist der *Drug Burden Index* (DBI), der anhand verabreichter Tagesdosen anticholinerger und sedierender Arzneimittel berechnet werden kann [31]. Eine deutsche Version des DBI, der *German Drug Burden Index* (GerDBI), wurde im Rahmen des „COFRAIL“ Projekts (Förderkennzeichen 01VSF17053) erstellt und stand während dieser Doktorarbeit vor Veröffentlichung zur Verfügung.

2.3 Entwicklung und Anwendung von prädiktiven Risikoscores

Risikoscores sind statistische Modelle, die auf klinischen, demografischen oder laborchemischen Risikofaktoren beruhen und dazu dienen, das individuelle zukünftige Erkrankungsrisiko eines Patienten vorherzusagen (prädiktive Risikoscores) oder das Vorliegen eines bestehenden klinischen Ereignisses zu erkennen (diagnostische Risikoscores). Neben der individuellen Prognose des Erkrankungsrisikos können prädiktive Risikoscores dazu genutzt werden, bei identifizierten Risikopatienten gezielte Präventionsmaßnahmen oder Therapiemodifikationen einzuleiten [32]. Im Gegensatz dazu werden diagnostische Scores verwendet, um eine schnelle und objektive Diagnosestellung bei bereits bestehenden klinischen Ereignissen basierend auf vorliegenden Symptomen und klinischen Befunden zu erleichtern [33, 34].

Es existieren verschiedene Modellierungsansätze für die Entwicklung von Risikoscores. Scores zur Vorhersage binärer Ereignisse werden häufig mittels multivariablen logistischen Regressionsmodellen entwickelt, die die Wahrscheinlichkeit für das Auftreten eines Ereignisses schätzen. Für die Vorhersage zeitabhängiger Ereignisse können Scores ausgehend von Cox Regressionsmodellen entwickelt werden [34]. Um die Vorhersage von logistischen Regressionsmodellen kontinuierlich zu optimieren und dynamische Risikoprognosen zu erhalten, können zudem komplexere statistische Verfahren wie die Bayes'sche Statistik oder maschinelles Lernen eingesetzt werden [35].

Bei der Entwicklung eines Scores werden geeignete Variablen unter Berücksichtigung von klinischer Relevanz, Verfügbarkeit und Multikollinearität ausgewählt und in ein statistisches Modell aufgenommen. Der Entwicklung folgt meist eine interne Validierung, bei der der entwickelte Score innerhalb der gleichen Kohorte angewandt wird, was durch Techniken wie s*plit-sample*, Kreuzvalidierung oder Bootstrapping-Verfahren umgesetzt werden kann [34]. Um die Übertragbarkeit des Scores auf andere Patientengruppen zu gewährleisten, ist eine externe Validierung entscheidend. Dabei wird der Score an einer unabhängigen Kohorte getestet [36].

Um den klinischen Nutzen eines Scores zu beurteilen, können Anforderungen an die Prädiktionsgenauigkeit und die klinische Anwendbarkeit herangezogen werden [37]. Die Prädiktionsgenauigkeit wird zum einen durch die statistischen Parameter Sensitivität, Spezifität, *positive predictive value* (PPV) und *negative predictive value* (NPV) beschrieben. Wichtig ist auch die Diskriminierungsfähigkeit des Scores, also die Fähigkeit zur Unterscheidung zwischen Patienten mit und ohne Ereignis, die durch die *area under the curve* (AUC) der *receiver operating characteristic* (ROC)-Kurve bestimmt wird [34]. Von Bedeutung ist zudem die Kalibrierung des Scores, die den Grad der Übereinstimmung zwischen vorhergesagtem und beobachtetem Risiko beschreibt [34]. Über die Prädiktionsgenauigkeit hinaus sind für die Eignung eines Scores jedoch

auch Aspekte der klinischen Anwendbarkeit entscheidend. Die Anwendung eines prognostischen Modells ist nur dann sinnvoll, wenn die Daten zur Erhebung des Scores routinemäßig zur Verfügung stehen, der Score einfach zu berechnen ist, das Ergebnis leicht interpretierbar ist und die klinische Entscheidungsfindung dadurch erleichtert wird [38].

Da zahlreiche prädisponierende und auslösende Risikofaktoren für das Delir bekannt sind und die Umsetzung von Präventionsmaßnahmen durch personelle, zeitliche und finanzielle Ressourcen begrenzt ist, bietet sich ein Screening nach Risikopatienten an, um verfügbare Ressourcen zu bündeln. Während allgemeine Präventionsmaßnahmen für alle älteren Patienten als sinnvoll erachtet werden, können spezifische Präventionsmaßnahmen nur für bestimmte Risikopatienten erforderlich sein. Ein systematischer Review von Lindroth et al. identifizierte 23 prädiktive Risikomodelle für Delir bei Patienten ≥ 60 Jahre in der Akutversorgung mit teilweiser interner oder externer Validierung [35]. Die Modelle wurden in unterschiedlichen Patientenpopulationen entwickelt und die häufigsten Risikofaktoren in extern validierten Modellen waren hohes Alter, eine vorbestehende kognitive Beeinträchtigung sowie eine funktionelle und sensorische Beeinträchtigung. Als Limitationen der Scores wurden die statistische Methodik, uneinheitliche Variablendefinitionen und inkonsistentes Delirscreening genannt. Ein systematischer Review von Kassie et al. zu Risikomodellen für Delir schlussfolgerte, dass präoperative Arzneimittel zwar ein häufig genannter und potenziell modifizierbarer Risikofaktor für das Delir sind, dieser Faktor aber in bereits entwickelten Risikomodellen nicht ausreichend berücksichtigt wird [39].

2.4 Die Arzneimittelanamnese bei stationärer Aufnahme

Die Kenntnis der vollständigen Medikation eines Patienten bildet die Grundlage für eine effektive und risikoreduzierte Arzneimittelversorgung im Krankenhaus. Voraussetzung hierfür ist die Durchführung einer strukturierten Arzneimittelanamnese, wodurch Medikationsfehler und unerwünschte Arzneimittelwirkungen während des stationären Aufenthalts reduziert werden [40]. Die meisten Verordnungsfehler treten zum Zeitpunkt der stationären Aufnahme auf, sind in 11-59 % der Fälle klinisch relevant und finden sich zu 40 % im Entlassbrief wieder [41, 42]. Auch die Aktualität eines bundeseinheitlichen Medikationsplans sollte bei stationärer Aufnahme überprüft werden, da Untersuchungen zufolge bei 78 % der Patienten Diskrepanzen zu einer strukturieren Arzneimittelanamnese bestehen [43].

Am Klinikum der Ludwig-Maximilians-Universität München wird routinemäßig Montag bis Freitag bei neu aufgenommenen chirurgischen Patienten eine pharmazeutische Arzneimittelanamnese durchgeführt. Hierbei wird eine bestmögliche Auflistung der verschreibungspflichtigen und freiverkäuflichen Arzneimittel des Patienten erfasst. Zusätzlich werden Indikationen und Interaktionen geprüft, Hinweise zu perioperativen Einnahmepause und Dosisanpassungen an Nieren- und Leberfunktion ergänzt und die Aufnahmemedikation auf die gelistete Hausmedikation umgestellt. Die Durchführung erfolgt zur Unterstützung der Stationen in Delegation der ärztlichen Tätigkeit. Die Vormedikation und ein Vorschlag für die stationäre Medikation werden in der elektronischen Patientenakte Meona® hinterlegt und vom Arzt geprüft, gegebenenfalls angepasst und angeordnet. Neben der Arzneimittelanamnese bei stationärer Aufnahme ist auch eine pharmazeutische Arzneimittelanamnese in der Anästhesieambulanz implementiert. Bei elektiven chirurgischen Patienten erfolgt hier üblicherweise 2-3 Wochen vor der geplanten Operation die Aufklärung der Anästhesie sowie eine Medikationserfassung.

Neben der Erhöhung der Arzneimitteltherapiesicherheit an der Schnittstelle zwischen ambulanter und stationärer Versorgung ist der Zeitpunkt der pharmazeutischen Arzneimittelanamnese geeignet, um Patienten mit einem erhöhten Risiko für postoperatives Delir anhand medikationsbezogener Faktoren zu identifizieren. Daher bietet sich die Entwicklung eines Risikoscores für dieses Setting an. Aufgrund der längeren Vorlaufzeit bis zur geplanten Operation ist der Zeitpunkt der pharmazeutischen Arzneimittelanamnese in der Anästhesieambulanz ebenfalls für ein Risikoscreening geeignet. Medikationsänderungen könnten zu diesem Zeitpunkt noch besser als bei stationärer Aufnahme initiiert werden, wenn eine Kommunikation mit dem ambulanten Verordner möglich ist. Mögliche Konsequenzen des Screenings würden das Informieren von pflegerischen und ärztlichen Kollegen sein sowie die Weitergabe von Anwendungshinweisen oder Umstellungsempfehlungen von Risikoarzneimitteln beinhalten.

2.5 Zielsetzung und Fragestellung

Das übergeordnete Ziel dieser Doktorarbeit war es zu evaluieren, wie Patienten mit einem erhöhten Risiko für ein postoperatives Delir bei stationärer Aufnahme zum Zeitpunkt der pharmazeutischen Arzneimittelanamnese identifiziert werden können. In diesem Zusammenhang wurden insbesondere Delirrisiko-erhöhende und anticholinerge Arzneimittel in der stationären Aufnahmemedikation sowie weitere verfügbare Risikofaktoren zum Zeitpunkt der Arzneimittelanamnese als Risikofaktoren für postoperatives Delir untersucht. Darauf aufbauend wurden ein prädiktiver Risikoscore entwickelt und validiert sowie unterschiedliche Verfahren zur Berechnung der anticholinergen Belastung miteinander verglichen.

Die zu beantwortenden Fragestellungen waren:

- Welche Risikofaktoren für postoperatives Delir sind zum Zeitpunkt der pharmazeutischen Arzneimittelanamnese verfügbar und können für ein routinemäßiges Screening nach Risikopatienten mithilfe eines Risikoscores genutzt werden?
- Sind Deliririsiko-erhöhende und anticholinerge Arzneimittel in der Aufnahmemedikation mit einem erhöhten Risiko für postoperatives Delir assoziiert?
- Sollte bei der Beurteilung der anticholinergen Belastung der Aufnahmemedikation als Risikofaktor für postoperatives Delir die Dosis der anticholinergen Arzneimittel berücksichtigt werden?

2.6 Inhalt der Veröffentlichungen

Im Rahmen der Doktorarbeit wurden zwei retrospektive Beobachtungsstudien durchgeführt, die sich mit der Identifizierung von Risikopatienten für postoperatives Delir in einem orthopädischen und unfallchirurgischen Patientenkollektiv beschäftigten. Ein positives Votum der Ethikkommission der Medizinischen Fakultät der LMU München liegt vor (23-0041).

In Veröffentlichung I wurde ein prädiktiver Risikoscore für postoperatives Delir zur Anwendung während der pharmazeutischen Arzneimittelanamnese an 546 orthopädischen und unfallchirurgischen Patienten ≥ 18 Jahre entwickelt und intern validiert. Die Validierung erfolgte nach einem *split-sample* Verfahren, sodass der Datensatz für Entwicklungskohorte (EntK) und Validierungskohorte (ValK) in einem 3:2 Verhältnis aufgeteilt wurde. Für die Entwicklung des Scores wurden potenzielle Risikofaktoren nach Verfügbarkeit und Eignung zum Zeitpunkt der Arzneimittelanamnese interprofessionell diskutiert. Basierend auf einem vorläufigen medikationsbasierten Risikoscore [44] wurden Delirrisiko-erhöhende Arzneimittelgruppen (*delirium risk-increasing drugs*) definiert. Potenzielle und geeignete Risikofaktoren wurden als

unabhängige Variablen in univariablen logistischen Regressionsanalysen für die abhängige Variable Auftreten eines postoperativen Delirs untersucht. Nach der Aufnahme signifikanter Risikofaktoren in ein multivariables logistisches Regressionsmodell wurde der Risikoscore basierend auf den Regressionskoeffizienten abgeleitet. Zur internen Validierung wurde der entwickelte Score auf die Patienten der Validierungskohorte angewandt. Die Score Validität wurde anhand von Parametern der Prädiktionsgenauigkeit (Sensitivität, Spezifität, PPV, NPV, AUC der ROC) für die EntK und ValK ermittelt.

Der Fokus von Veröffentlichung II lag auf der anticholinergen Belastung der stationären Aufnahmemedikation als prädisponierendem Risikofaktor für das postoperative Delir. Dabei handelte es sich um eine Subanalyse der Patienten > 65 Jahre des orthopädischen und unfallchirurgischen Patientenkollektivs der ersten Studie. Insgesamt wurden 385 Patienten in die Subanalyse eingeschlossen. Es wurde der Frage nachgegangen, ob die Dosis anticholinerger Arzneimittel bei der Beurteilung der anticholinergen Belastung der Aufnahmemedikation beim Screening auf postoperatives Delir berücksichtigt werden sollte. Zunächst wurde die ursprüngliche MARANTE-Skala durch ein Expertengremium um Dosiskonzepte für weitere anticholinerge Arzneistoffe zur *extended* MARANTE (extMARANTE)-Skala erweitert. Für den Vergleich wurden drei ACB-Scores herangezogen: der potenzbezogene GerACB-Score, die potenz- und dosisbezogene extMARANTE-Skala und der dosisbezogene GerDBI. Die Scores wurden hinsichtlich ihrer Prädiktionsgenauigkeit (Sensitivität, Spezifität, PPV und NPV), ihrer Bewertungsübereinstimmung mittels Kappa-Statistik und ihrer Assoziation mit postoperativem Delir mittels multivariabler Analyse untersucht und miteinander verglichen.

3. Zusammenfassung

Das postoperative Delir ist die häufigste Komplikation nach chirurgischen Eingriffen bei älteren Patienten und mit negativen Folgen wie einer verminderten funktionellen und kognitiven Leistungsfähigkeit sowie einer erhöhten Mortalität und Morbidität assoziiert. Aufgrund des demographischen Wandels und einer alternden Gesellschaft wird es auch in Zukunft notwendig sein, die begrenzten Ressourcen im Gesundheitssystem zu bündeln und alltagstaugliche Strategien zur Reduktion postoperativer Komplikationen bei älteren Patienten zu etablieren. Für die rechtzeitige Einleitung präventiver Maßnahmen ist die frühzeitige Identifizierung von Risikopatienten bei der stationären Aufnahme erforderlich, die durch die Anwendung von Risikoscores ermöglicht wird. Das Auftreten eines postoperativen Delirs wird durch zahlreiche prädisponierende und auslösende Risikofaktoren, darunter auch Arzneimittel, beeinflusst. Zu den prädisponierenden Risikofaktoren zählen Deliririsko-erhöhende und anticholinerge Arzneimittel in der Aufnahmemedikation. Vor diesem Hintergrund beleuchtet die vorliegende Doktorarbeit die Identifikation von Risikopatienten für ein postoperatives Delir zum Zeitpunkt der Arzneimittelanamnese anhand eines neu entwickelten prädiktiven Risikoscores und vergleicht darüber hinaus verschiedene Scores zur Erfassung der anticholinergen Belastung.

In Veröffentlichung I wurde ein prädiktiver Risikoscore für postoperatives Delir zur Anwendung in der pharmazeutischen Arzneimittelanamnese entwickelt, der die Aufnahmemedikation und weiteren verfügbaren Risikofaktoren berücksichtigt. Der Risikoscore mit *delirium risk-increasing drugs* (DRD-Score) enthält die vier Risikofaktoren Alter (> 65 Jahre, 2 Punkte; > 75 Jahre, 3 Punkte), eingeschränkte Nierenfunktion (< 60 ml/min/1,73 m^2, 1 Punkt), hohe anticholinerge Belastung (*German Anticholinergic Burden* [GerACB]-Score ≥ 3, 1 Punkt) und Einnahme von Deliririsko-erhöhenden Arzneimitteln (n ≥ 2, 2 Punkte). Patienten ab ≥ 4 Punkten wurden als Risikopatient klassifiziert. Die potenziellen Risikofaktoren männliches Geschlecht, Rauchen und erhöhter Alkoholkonsum [45] waren nicht signifikant mit dem Auftreten eines postoperativen Delirs assoziiert und wurden daher nicht in den Score aufgenommen. Insbesondere für Apotheker bietet der Score einen pragmatischen Ansatz zur schnellen Risikoeinschätzung von Patienten bei der stationären Aufnahme basierend auf den verfügbaren Medikations- und Labordaten.

Der Score erzielte eine gute bis moderate Sensitivität (Entwicklungskohorte [EntK] 83 %, Validierungskohorte [ValK] 63 %) und eine gute Spezifität (EntK 80 %, ValK 77 %). Etwa ein Drittel aller identifizierten Risikopatienten entwickelte ein postoperatives Delir (*positive predictive value* [PPV] EntK 38 %, ValK 31 %), während Nichtrisikopatienten mit hoher Wahrscheinlichkeit kein postoperatives Delir entwickelten (*negative predictive value* [NPV] EntK 97 %,

ValK 93 %). Die erforderlichen Risikofaktoren sind zum Zeitpunkt der Arzneimittelanamnese routinemäßig verfügbar und ein geschulter Apotheker kann die medikationsbezogenen Faktoren unkompliziert einschätzen. Bei der Erhebung des ACB-Scores können zudem Online-Rechner unterstützen [46]. Das Ziel des Screenings ist es, Patienten mit einem erhöhten Bedarf an pharmazeutischen Interventionen zu identifizieren. Als Konsequenz kann in der Arzneimittelanamnese ein verstärkter Fokus auf Interventionen bei identifizierten Risikopatienten liegen. Ein möglicher pharmazeutischer Beitrag sind Austauschempfehlungen bei zentral wirksamen anticholinergen Wirkstoffen, eine alters- und nierenfunktionsadaptierte Dosisprüfung sowie eine Überprüfung auf potenziell inadäquate Medikation im Alter. Darüber hinaus ist es sinnvoll, durch die Risikokommunikation mit Ärzten und Pflegenden allgemeine nicht-pharmakologische Präventionsmaßnahmen einzuleiten.

Eine Limitation des DRD-Scores ist, dass wichtige prädiktive Risikofaktoren wie Grunderkrankungen sowie funktionelle und kognitive Beeinträchtigungen nicht berücksichtigt werden. Dies lässt sich mit dem Anwendungsziel in der pharmazeutischen Arzneimittelanamnese und dem Fokus auf der Identifikation von Patienten mit pharmazeutischem Interventionsbedarf begründen. Da der DRD-Score in einem orthopädischen und unfallchirurgischen Patientenkollektiv entwickelt und intern validiert wurde, ist eine externe Validierung in einer anderen Patientenpopulation erforderlich, um die Prädiktionsgenauigkeit umfassender bewerten zu können.

Veröffentlichung II befasste sich mit der anticholinergen Belastung der Aufnahmemedikation als prädiktivem Risikofaktor für postoperatives Delir und ging der Frage nach, ob die Dosierung der Arzneimittel hierbei berücksichtigt werden sollte. Zu diesem Zweck wurden drei *anticholinergic burden* (ACB)-Scores miteinander vergleichen: der GerACB (potenzbezogen), die *extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure* (extMARANTE)-Skala (potenz- und dosisbezogen) und der *German Drug Burden Index* (GerDBI) (dosisbezogen). Insgesamt zeigte sich eine substanzielle Übereinstimmung in der Bewertung der Aufnahmemedikation durch die Scores (Interrater Reliabilität für Patienten mit und ohne postoperativem Delir $\kappa = 0{,}645$ und $\kappa = 0{,}632$). Für alle drei Scores war eine hohe Belastung signifikant mit dem Auftreten eines postoperativen Delirs in einer multivariablen Analyse assoziiert (adjustiert für Alter, Anzahl Arzneimittel in der Aufnahmemedikation, Demenz und *American Society of Anesthesiologists* Status). Bei der Verwendung als Screeninginstrument erzielten die Scores eine niedrige Sensitivität (GerACB 24 %, extMARANTE 42 %, GerDBI 41 %), eine hohe Spezifität (GerACB 94 %, extMARANTE 85 %, GerDBI 88 %), einen niedrigen PPV (GerACB 49 %, extMARANTE 39 %, GerDBI 43 %) und einen hohen NPV (GerACB 85 %, extMARANTE 87 %, GerDBI 87 %).

Die drei ACB-Scores sind aufgrund ihrer niedrigen Sensitivität und ihres geringen PPV als alleinige Screeninginstrumente für postoperatives Delir nicht geeignet, obwohl eine hohe Belastung signifikant mit postoperativem Delir assoziiert war. Dies unterstreicht die Notwendigkeit, die anticholinerge Belastung in Kombination mit weiteren Risikofaktoren für das postoperative Delir zu bewerten, wie beispielsweise durch den DRD-Score. Die zusätzliche Berücksichtigung der Dosis geht mit einer aufwändigeren Scoreberechnung einher, während sich die Bewertung der anticholinergen Belastung dadurch nur geringfügig ändert. Der einfache GerACB erzielte zwar die geringste Sensitivität, aber auch die höchste Spezifität und den höchsten PPV. Für eine einfache und pragmatische Überprüfung der anticholinergen Belastung der Aufnahmemedikation bleibt der GerACB somit ausreichend. Bei Patienten > 65 Jahre mit hoher anticholinerger Belastung sollten potenzielle Austauschmöglichkeiten, insbesondere von zentral wirksamen anticholinergen Wirkstoffen, evaluiert werden. Auch wenn in dieser Studie eine Dosisberücksichtigung bei Berechnung der anticholinergen Belastung als nicht notwendig bewertet wurde, sollte bei der Medikationsanalyse eine alters- und nierenfunktionsadaptierte Dosis überprüft werden.

Zusammenfassend wurden in dieser Doktorarbeit Möglichkeiten zur Identifizierung von Risikopatienten für postoperatives Delir bei stationärer Aufnahme anhand ihrer Medikation evaluiert. Delirrisiko-erhöhende und anticholinerge Arzneimittel in der Aufnahmemedikation sind für Patienten > 65 Jahre, insbesondere mit einer eingeschränkten Nierenfunktion, prädiktive und potenziell modifizierbare Risikofaktoren für postoperatives Delir. Die Berücksichtigung der Dosis anticholinerger Arzneimittel durch dosisbezogene ACB-Scores ist nicht erforderlich, die Verwendung eines einfachen potenzbasierten ACB-Scores ist ausreichend. Arzneimittel als prädiktive Risikofaktoren und die Anwendung des DRD-Scores und der ACB-Scores müssen im Kontext des multifaktoriellen Geschehens beim postoperativen Delir mit weiteren prädiktiven und auslösenden Risikofaktoren betrachtet werden. Damit ist eine moderate Sensitivität der Scores akzeptabel und mögliche pharmazeutische sowie nicht-pharmakologische Präventionsmaßnahmen sollten für Risikopatienten abgeleitet und umgesetzt werden. Sowohl der DRD- als auch die ACB-Scores erreichten eine hohe Spezifität, so dass bei Fehlen der medikationsbezogenen Risikofaktoren ein postoperatives Delir nur selten auftrat und pharmazeutischer Interventionsbedarf bei der Aufnahmemedikation nicht häufig erforderlich sein sollte. Als Ausblick zu dieser Arbeit sollte untersucht werden, ob Risikopatienten laut des DRD-Scores einen erhöhten Interventionsbedarf in ihrer Medikation aufweisen, welche pharmazeutischen Interventionen erforderlich sind und ob es möglich und sinnvoll ist, diese Interventionen im präoperativen Setting umzusetzen.

4. Abstract (English)

Postoperative delirium is the most common complication following surgical procedures in older adult patients and is associated with adverse outcomes such as functional and cognitive decline and increased mortality and morbidity. With demographic changes and an aging society, there is a need to develop practical strategies that take limited healthcare resources into account to reduce postoperative complications in older patients. Early identification of patients at risk upon hospital admission is necessary for timely initiation of preventive measures, which is made possible by the use of risk scores. The development of postoperative delirium is influenced by numerous predisposing and precipitating factors, including drugs. Delirium risk-increasing and anticholinergic drugs in the admission medication are examples of predisposing risk factors. Following this, this dissertation investigates the identification of patients at risk for postoperative delirium at the time of medication reconciliation using a newly developed predictive risk score and compares different scores for assessing anticholinergic burden.

In publication I, a predictive risk score for postoperative delirium was developed for use during pharmacist-led medication reconciliation based on admission medication and other available risk factors. The risk score including delirium risk-increasing drugs (DRD score) considers four risk factors: age (> 65 years, 2 points; > 75 years, 3 points), reduced kidney function (< 60 ml/min/1.73 m^2, 1 point), high anticholinergic burden (German Anticholinergic Burden [GerACB] score ≥ 3, 1 point), and use of delirium risk-increasing drugs (≥ 2, 2 points). Patients with a score ≥ 4 points were classified as risk patients. The potential risk factors male gender, smoking, and heavy alcohol consumption [45] were not significantly associated with postoperative delirium and were therefore not included in the final score. For pharmacists in particular, the DRD score provides a pragmatic approach for rapid risk assessment of patients upon hospital admission, based on available medication and laboratory data.

The score achieved good to moderate sensitivity (development cohort [DevC] 83%, validation cohort [ValC] 63%) and good specificity (DevC 80%, ValC 77%). Approximately one-third of identified risk patients developed postoperative delirium (positive predictive value [PPV] DevC 38%, ValC 31%), whereas non-risk patients were unlikely to develop postoperative delirium (negative predictive value [NPV] DevC 97%, ValC 93%). The required risk factors are routinely available during medication reconciliation and a trained pharmacist can easily evaluate medication-related factors. Online calculators may also assist in calculating the ACB score [46]. The aim of the screening is to identify patients with an increased need for pharmaceutical interventions. Consequently, pharmacists can focus on interventions for identified risk patients during medication reconciliation. Possible contributions by pharmacists include recommendations for

replacing drugs with central anticholinergic effects, reviewing drug doses according to age and kidney function, and checking for potentially inadequate medication for older patients. In addition, general non-pharmacological preventive measures could be initiated through risk communication with doctors and nurses.

A limitation of the DRD score is that other important risk factors, such as underlying diseases and functional and cognitive impairment, were not included. This is due to the focus on assessment during medication reconciliation with the aim of identifying patients who might benefit the most from drug safety recommendations. As the DRD score has been developed and internally validated in an orthopaedic and trauma surgery cohort, external validation in other patient populations is needed to broadly assess its predictive accuracy.

Publication II addressed anticholinergic burden in admission medication as a predictive risk factor for postoperative delirium and investigated whether the drug dose should be taken into account. Three anticholinergic burden (ACB) scores were compared: the GerACB (potency-related), the extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (extMARANTE) scale (potency- and dose-related) and the German Drug Burden Index (GerDBI) (dose-related). Overall, there was substantial agreement in the assessment of admission medication by the scores (interrater reliability for patients with and without postoperative delirium $\kappa = 0.645$ and $\kappa = 0.632$). For all three scores, a high burden was significantly associated with postoperative delirium in a multivariable analysis (adjusted for age, number of drugs in the admission medication, dementia, and American Society of Anesthesiologists status). When used as a screening tool, the scores achieved low sensitivity (GerACB 24%, extMARANTE 42%, GerDBI 41%), high specificity (GerACB 94%, extMARANTE 85%, GerDBI 88%), low PPV (GerACB 49%, extMARANTE 39%, GerDBI 43%) and high NPV (GerACB 85%, extMARANTE 87%, GerDBI 87%).

The results indicate that due to their low sensitivity and PPV, none of the three ACB scores are suitable as stand-alone screening tools for postoperative delirium, although there was a significant association between a high burden and postoperative delirium. This emphasises the need to evaluate the anticholinergic burden alongside other risk factors for delirium, as with the DRD score. Additional dose consideration requires a more complex calculation, whereas medication assessment changes only slightly. The simple GerACB score had the lowest sensitivity but the highest specificity and PPV, making it sufficient for pragmatic screening of admission medication. In patients aged > 65 years with a high anticholinergic burden, potential substitution of drugs should be evaluated, especially for drugs with central anticholinergic effects. Although dose consideration using dose-related ACB scores was not deemed necessary in this study, age- and renal function-adjusted dosing should be checked during medication analysis.

In summary, this dissertation evaluated methods to identify patients at risk for postoperative delirium at hospital admission based on their admission medication. Delirium risk-increasing and anticholinergic drugs in admission medication are predictive and potentially modifiable risk factors for postoperative delirium in patients aged > 65 years, especially in those with impaired renal function. The use of dose-related ACB scores is not necessary, and a simple potency-based ACB score remains sufficient for screening a patient's medication. The impact of drugs as predictive risk factors and the use of the DRD and ACB scores must be evaluated in the context of the multifactorial aetiology of delirium, along with other predictive and precipitating risk factors. Therefore, a moderate sensitivity of the scores is acceptable, and potential pharmaceutical and non-pharmacological preventive measures should be derived and implemented for patients at risk. Both the DRD and ACB scores achieved high specificity, meaning that in the absence of medication-related risk factors, postoperative delirium is rare and pharmaceutical interventions regarding the admission medication should not be required frequently. Further investigations should determine whether risk patients according to the DRD score have an increased need for interventions in their medication, which pharmaceutical interventions are necessary, and whether it is possible and feasible to implement these interventions in the preoperative setting.

5. Veröffentlichung I

Development and validation of a new drug-focused predictive risk score for postoperative delirium in orthopaedic and trauma surgery patients

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Development and validation of a new drug-focused predictive risk score for postoperative delirium in orthopaedic and trauma surgery patients

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Abstract

Background Postoperative delirium (POD) is the most common complication following surgery in elderly patients. During pharmacist-led medication reconciliation (PhMR), a predictive risk score considering delirium risk-increasing drugs and other available risk factors could help to identify risk patients.

Methods Orthopaedic and trauma surgery patients aged ≥ 18 years with PhMR were included in a retrospective observational single-centre study 03/2022-10/2022. The study cohort was randomly split into a development and a validation cohort (6:4 ratio). POD was assessed through the 4 A's test (4AT), delirium diagnosis, and chart review. Potential risk factors available at PhMR were tested via univariable analysis. Significant variables were added to a multivariable logistic regression model. Based on the regression coefficients, a risk score for POD including delirium risk-increasing drugs (DRD score) was established.

Results POD occurred in 42/328 (12.8%) and 30/218 (13.8%) patients in the development and validation cohorts, respectively. Of the seven evaluated risk factors, four were ultimately tested in a multivariable logistic regression model. The final DRD score included age (66–75 years, 2 points; > 75 years, 3 points), renal impairment (eGFR < 60 ml/min/1.73m^2, 1 point), anticholinergic burden (ACB-score ≥ 3, 1 point), and delirium risk-increasing drugs ($n \geq 2$; 2 points). Patients with ≥ 4 points were classified as having a high risk for POD. The areas under the receiver operating characteristic curve of the risk score model were 0.89 and 0.81 for the development and the validation cohorts, respectively.

Conclusion The DRD score is a predictive risk score assessable during PhMR and can identify patients at risk for POD. Specific preventive measures concerning drug therapy safety and non-pharmacological actions should be implemented for identified risk patients.

Keywords Medication Safety, Geriatrics, Screening tools, Postoperative delirium

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Introduction

Delirium is defined as an acute change in attention, awareness, and cognition [1]. It usually develops rapidly with a fluctuating course [1]. In elderly, hospitalized patients, it represents a severe complication with a prevalence ranging from 20% in general surgery up to 70% in intensive care units [2, 3]. After surgical intervention, postoperative delirium (POD) is one of the most common complications [4]. The clinical consequences of delirium are severe with an increase in mortality, length of hospital stay, and development of dementia or cognitive decline [5, 6].

Multiple risk factors determine the risk for delirium. Predisposing risk factors include advanced age, visual and hearing impairment, history of prior delirium, cognitive impairment, frailty, and comorbidities (i.e. cardiovascular or renal diseases). In addition, precipitating factors such as acute medical illness (i.e. infections, hypoglycaemia), trauma, surgical procedures, dehydration, pain, medication use, and drug withdrawal are relevant [2]. Preventive measures can reduce the occurrence of delirium; therefore, overall non-pharmacological measures are recommended for vulnerable patients [2, 7]. However, identifying patients at risk who are most likely to benefit from specific preventive measures remains challenging. One approach is the use of risk prediction scores based on pre- and perioperative risk factors for the identification of patients at high risk for delirium.

Drugs, especially substances targeting the central nervous system, are a proven risk factor for in-hospital delirium [8–11]. However, a recent systematic review found that medication is not adequately considered in previously developed risk scores and should be addressed in future models [12]. Existing risk scores already considering medication include the risk factors polymedication (≥five regular drugs) [13], psychoactive and anticholinergic drugs [14], or medication for insomnia treatment [15]. The Delirium Model (DEMO) includes drugs associated with delirium in a linear prediction model [16]. Recently, a medication-based prediction score for POD in surgical patients was developed by our group [17]; however, further revision concerning the weighing of risk factors and testing of the predictive performance is needed.

Importantly, patients at risk for POD should be identified at an early stage prior to surgery. One opportunity for a timely identification of patients at risk for drug-related POD is during pharmacist-led medication reconciliation (PhMR) at hospital admission. In addition, scores including delirium risk-increasing drugs should be easy to use for pharmacists involved in the hospital medication process, and variables should be readily accessible in clinical practice. Consequently, pharmacists can inform physicians about the patients' individual risk and make preventive suggestions with a focus on minimizing the risk for drug-related POD.

Therefore, the aim of our study was to further develop and validate a risk score for POD including delirium risk-increasing drugs, which can be performed during PhMR at hospital admission by pharmacists based on the admission medication and other available risk factors. This risk score could identify patients at risk for drug-related POD benefiting from suggestions for drug therapy safety and additional preventive measures.

Methods

Study design

A retrospective single-centre cohort study was conducted at LMU University Hospital Munich, a tertiary care hospital, from March to October 2022. Ethics approval was obtained from the Ethics Committee of LMU University Hospital Munich (No. 23–0041). Three orthopedic or trauma surgery wards were included, which were part of a pilot project focused on reducing postoperative complications in elderly patients, specifically delirium (gertrud program - age-appropriate proactive health care) [18]. Ward staff (physicians, nurses, and physiotherapists) was especially trained for delirium awareness, and trained nurses regularly performed delirium assessments using the 4 A's test (4AT) [19]. For patients with a 4AT score ≥ 4, physicians confirmed the result, and if delirium was present, a diagnosis was documented according to the International Classification of Diseases 10th revision (ICD-10) [20].

The inclusion criteria for our study were age ≥ 18 years, surgical procedure in orthopaedics or trauma surgery, and a pharmacist-led medication reconciliation (PhMR) at hospital admission. Patients with preoperative delirium, delirium due to alcohol withdrawal, or cases with missing data were excluded from the analysis.

PhMR at LMU University Hospital is routinely performed for all admitted surgical patients from Monday to Friday to assess a detailed drug history and generate a medication list with prescribed and over-the-counter drugs. In addition, smoking status and alcohol use are assessed according to self-reports. Information is saved in the electronic medication record Meona® (Mesalvo GmbH Freiburg, Germany).

Identification of potential preoperative risk factors

The previously established medication-based prediction score for POD in surgical patients developed by our group included age (≥65 years; ≥ 75 years), male sex, renal impairment (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2), hepatic impairment (model of endstage liver disease (MELD) score 10–14; ≥ 15 [21]), delirium risk-increasing drugs (antidiabetics, opioids, antiepileptic drugs, anti-Parkinson drugs, antipsychotic

drugs, hypnotics and sedatives including benzodiazepines, antidepressant drugs, anti-dementia drugs, and antihistamines for systemic use), and anticholinergic burden (ACB score ≥ 3 [22]) [17]. The ACB score is an established score summing up the anticholinergic properties of a patient's medication; drugs are assigned no (0), weak (1), moderate (2), or strong (3) anticholinergic effects. A literature search was performed on additional risk factors for delirium and risk factors included in other published prediction scores. The identified risk factors were evaluated for availability at the time of PhMR, and a consensus for inclusion in the prediction score was reached following interprofessional discussion by neurologists, geriatricians, anaesthesiologists, and pharmacists.

Data collection

All patient information, admission medication, laboratory data (eGFR calculated by the CKD-EPI equation [ml/min/1.73 m^2] [23]), alcohol use, and smoking status were collected from electronic health records (i.s.h.med®, Cerner Corporation, North Kansas City, USA) and Meona® as assessed during PhMR. Alcohol use was classified according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [24]. Smoking status was documented as 'yes' or 'no' regardless of the units consumed per day (cigarettes, cigars, vaporizers). The anticholinergic burden was calculated with the ACB score for drugs available in Germany [22]. Data was documented using Microsoft Excel® 2016 (Seattle, WA, USA).

Retrospective assessment of delirium diagnoses

POD was assessed for all study patients based on the documented 4AT scores, ICD-10 diagnoses (F05.0, F05.1, F05.8, F05.9 [20]), and a subsequent chart review. A physician confirmed the initial assessment by a pharmacist. In addition, a chart review, as validated in previous studies, was conducted [25, 26] (keywords: delirious, confusion, disoriented, disturbed attention, hallucination, restless, and agitated [16, 27]).

Statistical analysis

A study size of 550 patients was calculated for ten outcome events per variable [28], seven risk factors and an estimated overall POD prevalence of 12% [29]. Statistical analysis was performed with SPSS Statistics® version 29.0 (IBM Corp., Armonk, NY, USA). For descriptive statistics, categorical variables were expressed in absolute and relative frequencies and compared using Chi^2-Test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR). Comparisons were made by Student's t-test or Mann-Whitney U test as appropriate. *P* values were two-sided, and values < 0.05 were considered statistically significant. Figures were created using Adobe Illustrator® version 27.0 (San Jose, CA, USA).

Score development and validation

For the development and internal validation of the predictive score for drug-related POD, the cohort was divided into two cohorts by random allocation (split-sample validation approach, 6:4 allocation), and patients were randomly assigned to either cohort through computerized random numbers using Microsoft Excel® 2016 (Seattle, WS, USA).

For the development cohort, univariable logistic regression analysis was used to evaluate the associations between continuous or categorical variables and the presence or absence of POD. Continuous variables were transformed into categorical variables by using suitable cut-off values determined through clinically established definitions for chronic kidney disease [23], geriatric age > 65 years [30] and high anticholinergic burden with an ACB score ≥ 3 [22]. If appropriate, the Youden index of receiver operating characteristic (ROC) analysis was also used.

Statistically significant variables ($p < 0.05$) from univariable logistic regression analysis were added to a multivariable forward stepwise logistic regression model. For derivation of the score, the weighting point for each variable was defined by the corresponding regression coefficient rounded to the nearest integer. The area under the curve (AUC) was obtained through ROC analysis. Optimal cut-off values were determined through the Youden index. Goodness of fit was assessed using the Hosmer-Lemeshow test ($p > 0.05$, good fit), and multicollinearity of variables was reviewed through a correlation matrix.

For validation, the derived score was applied to the patients in the validation cohort, and the corresponding AUC was determined. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated. The calibration of the model was assessed by plotting a function of the predicted risks against the observed risks.

Results

Definition of potential preoperative risk factors

Based on the previously developed medication-based prediction score [17], a renewed literature review, and interprofessional discussions, seven potential risk factors for drug-related POD were established (Table 1). Additional potential risk factors included for further analysis were heavy alcohol use [13, 31–33], daily smoking [14, 25, 31], and inhalants for chronic obstructive airway disease [34]. Due to the large number of missing laboratory values, the MELD score [21] was excluded.

Table 1 Definition of potential risk factors for POD available at pharmacist led medication reconciliation [13, 14, 17, 25, 31–34]

Potential risk factor		Comment
Age [years]		
Sex [male/female]		
Kidney function (eGFR) [ml/min/1.73m^2]		
Delirium risk-increasing drugs [n]	ATC code	Number of drugs for regular and on demand medication
Anti-dementia drugs	N06D	
Antidepressants	N06A	Also for treatment of neuropathic pain
Antiepileptic drugs	N03	Also for treatment of neuropathic pain
Antipsychotics	N05A	
Anti-Parkinson drugs	N04	Also for treatment of restless legs syndrome
Anxiolytics (benzodiazepines)	N05BA	
Hypnotics and sedatives	N05C	
Opioids	N02A	
Antihistamines for systemic use	R06	
Antidiabetics	A10	Oral antidiabetics/GLP-1 analogues summed up as 1 drug; insulins and analogues summed up as 1 drug
Inhalants for chronic obstructive airway disease (COPD)	R03AL, R03BB	Adrenergic + LAMA (+ ICS), LAMA
Anticholinergic burden [ACB score] [22]		
Heavy alcohol use [24] [yes/no]		men (> 14 standard drinks per week/> 4 drinks any day); women (> 7 standard drinks per week/> 3 drinks any day)
Smoking status [yes/no]		Daily smoking of cigarettes (based on self-report)

POD = postoperative delirium; eGFR = estimated glomerular filtration rate; ATC code = Anatomical Therapeutic Chemical code; GLP-1 = Glucagon-like Peptide 1; LAMA = long-acting muscarinic receptor antagonist; ICS = inhaled corticosteroid

Characterization of the retrospective patient cohort

During the study period, 804 patients were initially screened for inclusion. The inclusion criteria were not met by 218 patients (missing PhMR, $n=56$; no surgical intervention in orthopaedics or trauma surgery, $n=162$). A total of 40 patients were excluded due to missing laboratory values ($n=38$), preoperative delirium ($n=1$), or delirium due to alcohol withdrawal ($n=1$). Overall, 546 patients (median age 74 years (IQR 64–82), 45.2% male) were included and randomly divided into development (60%, $n=328$) and validation (40%, $n=218$) cohorts. Table 2 shows the patient characteristics, prevalence of POD, and potential risk factors associated with delirium for both study cohorts. A full overview of the observed drug classes of delirium risk-increasing drugs can be found in Supplementary Table S1.

Development of a predictive risk score for POD including delirium risk-increasing drugs

Univariable logistic regression analysis was performed for all potential risk factors and the presence or absence of delirium. The continuous variables age, eGFR, ACB score, and number of delirium risk-increasing drugs were significantly associated with the development of POD ($p<0.001$). The risk factors not significant and thus excluded from further calculations were sex ($p=0.465$), heavy alcohol use ($p=0.183$), and smoking status ($p=0.467$).

Significant continuous factors were transformed into categorical variables based on suitable cut-off values determined through clinically established definitions or the Youden index of ROC analysis (number of delirium risk-increasing drugs = 1.5; age = 73.5 years; eGFR = 58.5 ml/min/1.73m^2) rounded to a reasonable value. The final categorical variables were age 66–75 years ($p=0.02$), age > 75 years ($p<0.001$), eGFR < 60 ml/min/1.73m^2 ($p<0.001$), ACB score ≥ 3 ($p<0.001$), and ≥ two delirium risk-increasing drugs ($p<0.001$).

These significant variables were further included in a multivariable forward stepwise logistic regression model. For derivation of the score, the corresponding regression coefficients were rounded to the nearest integer (Table 3). In this manuscript, this new score will be called the DRD score (risk score for POD including Delirium risk-increasing Drugs). Correlations between predictor variables were low ($r<0.8$), indicating no multicollinearity [35]. The AUCs of the ROC curves of the logistic regression model and the derived DRD score are shown in Fig. 1a. The Hosmer-Lemeshow test indicated a good model fit ($p=0.602$). Figure 1b shows the calibration plot comparing the predicted and observed POD risk. The optimal cut-off value for discriminating between patients at high and low risk for POD according to the Youden index was 3.5 points. Therefore, we classified patients at risk for drug-related POD who received ≥ 4 points.

Table 2 Patient characteristics and potential risk factors associated with POD in the development and validation cohorts of patients with or without POD

Variable	Development cohort ($n=328$)			Validation cohort ($n=218$)		
POD	no	yes	*p*	no	yes	*p*
	286 (87.2)	42 (12.8)		188 (86.2)	30 (13.8)	
Age [years]	72 (61–81)	84 (76–90)	< 0.001[a]	73 (62–81)	87 (81–89)	< 0.001[a]
Sex						
female	153 (53.5)	25 (59.5)	0.464[b]	105 (55.9)	16 (53.3)	0.797[b]
male	133 (46.5)	17 (40.5)		83 (44.1)	14 (46.7)	
eGFR [ml/min/1.73m^2]	80 (65–93)	55 (38–80)	< 0.001[a]	81 (66–91)	60 (35–82)	< 0.001[a]
ACB score	0 (0–1)	2 (0–3)	< 0.001[a]	0 (0–1)	1 (0–3)	0.001[a]
ACB score ≥ 3 [n]	20 (7.0)	12 (28.6)	< 0.001[b]	15 (8.0)	8 (26.7)	0.002[b]
Delirium risk-increasing drugs per patient [n]	0 (0–1)	2 (0–3)[c]	< 0.001[a]	0 (0–1)	1 (0–2)[d]	0.008[a]
Intake of delirium risk-increasing drugs [n]	98 (34.3)	33 (78.6)	< 0.001[b]	77 (41.0)	19 (63.3)	0.022[b]
Heavy alcohol use						
yes	28 (9.8)	7 (16.7)	0.178[b]	22 (11.7)	4 (13.3)	0.798[b]
no	258 (90.2)	35 (83.3)		166 (88.3)	26 (86.7)	
Smoking status						
yes	31 (10.8)	3 (7.1)	0.463[b]	16 (8.5)	2 (6.7)	0.733[b]
no	255 (89.2)	39 (92.9)		172 (91.5)	28 (93.3)	

Values are expressed as number (%) or median (interquartile range)

a Mann-Whitney U test comparing patients with and without POD

b Chi^2-Test comparing patients with and without POD

c The following top 5 drug classes were observed: antidepressants (22.5%), opioids (14.6%), antiepileptic drugs (11.2%), antipsychotics (10.1%), and anti-Parkinson drugs (10.1%)

d The following top 5 drug classes were observed: antidepressants (19.0%), anti-Parkinson drugs (14.3%), opioids (11.9%), antiepileptic drugs (11.9%), and antipsychotics (11.9%)

POD = postoperative delirium; eGFR = estimated glomerular filtration rate; ACB = anticholinergic burden

Table 3 Independent risk factors for postoperative delirium identified by multivariable logistic regression analysis

Risk factor	Category	Regression coefficient	Odds Ratio (95% CI)	*p*	Points assigned
Age [years]	≤ 65		1		0
	66–75	2.41	11.15 (1.25–99.10)	0.03	2
	> 75	3.17	23.91 (2.80-204.26)	0.004	3
eGFR [ml/min/1.73m^2]	≥ 60		1		0
	< 60	1.36	3.89 (1.21–12.11)	0.001	1
ACB score	< 3		1		0
	≥ 3	1.34	3.83 (1.21–12.11)	0.02	1
Delirium risk-increasing drugs [n]	< 2		1		0
	≥ 2	1.68	5.38 (2.28–12.65)	< 0.001	2

CI = confidence interval; eGFR = estimated glomerular filtration rate; ACB = anticholinergic burden

Validation of the predictive risk score for POD including delirium risk-increasing drugs

To validate the developed risk score, we retrospectively applied the DRD score to each patient in the validation cohort. The AUC of the ROC curve of the validation cohort based on the risk score and the calibration plot are shown in Fig. 1c and d. There were no statistically significant differences between the patient characteristics of both cohorts in terms of the distribution of preoperative risk factors included in the developed score, as shown in Table 4. The sensitivity, specificity, PPV, NPV, and likelihood ratios for the DRD score were calculated for both the development and validation cohort and are shown in Table 5.

Discussion

We developed and validated a new predictive risk score for postoperative delirium including delirium risk-increasing drugs (DRD score) based on preoperative risk factors available during pharmacist-led medication reconciliation at hospital admission. In a retrospective single-centre study including orthopaedic and trauma surgery patients, the four risk factors advanced age, reduced kidney function, high anticholinergic burden, and number of delirium risk-increasing drugs proved to be predictive in the final model after multivariable logistic regression analysis. The sensitivity of the score was good with 83.3% in the development and fair with 63.3% in the validation cohort, also a good specificity was

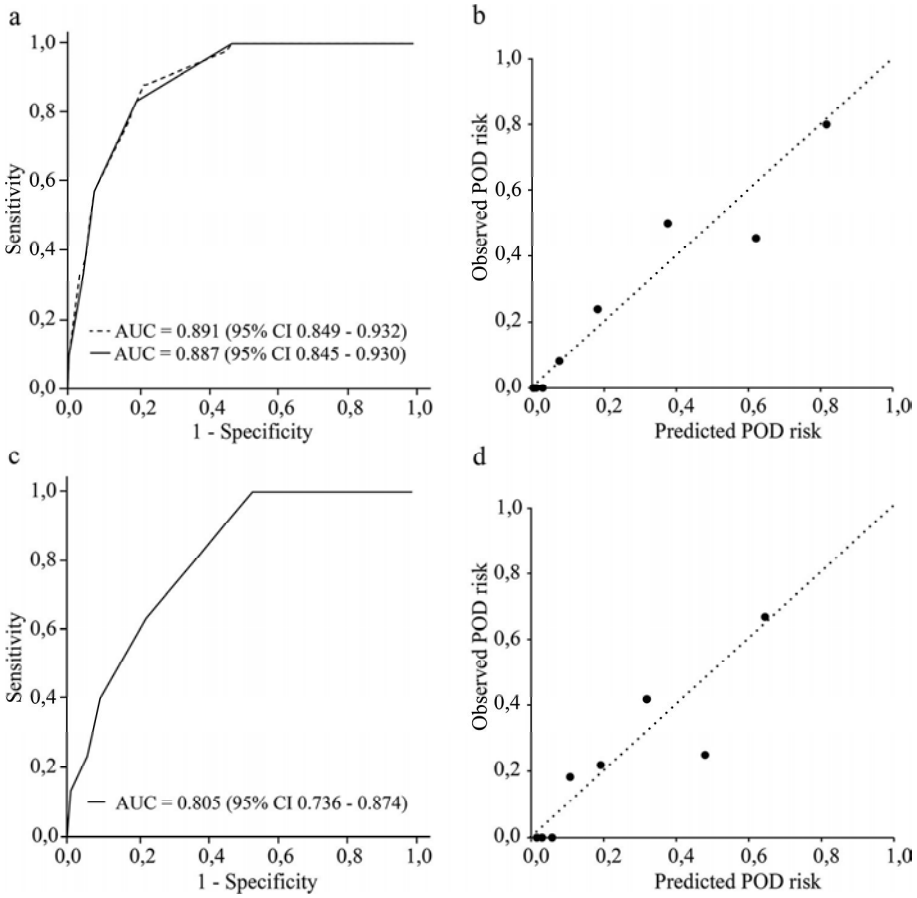

Fig. 1 Receiver operating characteristic (ROC) curve, calculated area under the curve (AUC), and calibration plot for development and validation cohort. (**a**) Development cohort, (dotted line, ROC curve of the logistic regression model; solid line, ROC curve of the DRD score). (**b**) Development cohort, calibration plot comparing the predicted POD risk and observed POD risk. Patients were grouped into 8 groups of predicted risk according to the DRD score (0–7 points), the identity line is shown as dashed line. (**c**) Validation cohort, ROC curve of the DRD score. (**d**) Validation cohort, calibration plot
AUC = area under the curve; ROC = receiver operating characteristic; CI = confidence interval; POD = postoperative delirium

Table 4 Homogeneity between the development and validation cohorts for preoperative risk factors

Preoperative risk factor	Development cohort (*n* = 328)	Validation cohort (*n* = 218)	*p*
Age [years]			0.373
≤ 65	100 (30.5)	60 (27.5)	
66–75	84 (25.6)	49 (22.5)	
> 75	144 (43.9)	109 (50.0)	
eGFR [ml/min/1.73m^2]			0.983
≥ 60	248 (75.6)	165 (75.7)	
< 60	80 (24.4)	53 (24.3)	
ACB score			0.763
< 3	296 (90.2)	195 (89.4)	
≥ 3	32 (9.8)	23 (10.6)	
Delirium risk-increasing drugs [n]			0.588
< 2	265 (80.8)	172 (78.9)	
≥ 2	63 (19.2)	46 (21.1)	

Values are expressed as number (%)

eGFR = estimated glomerular filtration rate; ACB = anticholinergic burden

Table 5 Performance of the predictive DRD score

	Development cohort ($n=328$)		Validation cohort ($n=218$)	
POD	Yes 42 (12.8)	No 286 (87.2)	Yes 30 (13.8)	No 188 (86.2)
High risk of POD (score ≥ 4)	35	57	19	43
Low risk of POD (score < 4)	7	229	11	145
Sensitivity (%)	83.3		63.3	
Specificity (%)	80.1		77.1	
Positive predictive value (%)	38.0		30.6	
Negative predictive value (%)	97.0		92.9	
Positive Likelihood ratio (LR+)	4.1		2.8	
Negative Likelihood ratio (LR-)	0.2		0.5	

Values are expressed as absolute number or number (%)

POD = postoperative delirium

achieved with 80.1% and 77.1%, respectively. Thus, the newly developed DRD score is a promising tool for the early and pragmatic identification of patients at risk for POD. After calculation during medication reconciliation at admission it allows a timely initiation of preventive measures. Considering the severe clinical consequences of POD and that 40% of delirium cases are possibly preventable [30], implementation of the score in the clinical routine has the potential to considerably improve patient safety.

Drugs are a well-described risk factor for delirium. Psychoactive drugs and drugs associated with brain-related adverse effects are commonly known and possibly modifiable risk factors for delirium [11, 14, 36]. Surprisingly, in several predictive risk scores developed in recent years, drugs are mostly neglected [25, 32, 33, 37], although medications may account for 12–39% of delirium cases [38]. Risk scores including drugs either require complex automated calculations [16] or show an oversimplified approach when only considering polymedication (≥ five regular drugs) [13]. Our list of delirium risk-increasing drugs includes drugs with effects on the central nervous system as well as drugs correlating with comorbidities associated with delirium (i.e. diabetes mellitus and COPD) [14, 34, 39]. In our analysis, we found that taking two or more delirium risk-increasing drugs was a significant risk factor for POD (OR 5.38, 95% CI 2.28–12.65). Identifying these drugs during PhMR appears feasible and easily applicable in clinical practice.

Neurotransmitter disturbance is a major mechanism in delirium pathophysiology, and a reduced cholinergic activity is associated with altered attention and delirium [2]. Anticholinergic drugs that decrease central cholinergic activity can therefore increase the risk for delirium. This anticholinergic activity can be estimated through anticholinergic burden scales. A preoperative high anticholinergic burden is significantly associated with incident delirium [40–42], although contrary findings with no association have been reported in other studies [43]. Our study determined that a high anticholinergic burden was significantly associated with POD in both univariable and multivariable analyses.

Advanced age is a well-known risk factor for delirium [2, 7] and, accordingly, was proven to be a statistically significant factor in our study, as confirmed by multivariable analysis. However, thresholds for age as a risk factor vary in risk scores and evaluations published so far. In our study, two thresholds were evident: 66–75 years of age (OR 11.15) and >75 years of age (OR 23.91); both of these thresholds were included in the score with distinct point assignments.

We found that a moderately decreased kidney function (eGFR < 60 ml/min/1.73m^2) on the day of admission was significantly associated with POD (OR 3.89, 95% CI 1.21–12.11). To our knowledge, this predictor has not been considered in previously developed risk scores. An association between moderate renal impairment (eGFR 30–60 ml/min/1.73m^2, calculated using cystatin-based equations) and delirium was found in fracture patients aged 75–84 years [44]. End-stage renal failure was a consistent risk factor for POD, as reported in an umbrella review of systematic reviews [45]. We used a creatinine-based CKD-EPI equation to calculate the eGFR and found that moderately decreased values were associated with delirium.

Although male gender is included in previously developed risk scores [33, 37, 46], we did not determine this factor to be significant. The predictors smoking and heavy alcohol use are also represented in published risk models [14, 25, 32, 33], whereas for our cohort no associations were found. Underreporting might be a reason for this finding since documentation was based on self-reports. Although the exact correlation between smoking and delirium is unclear, acute nicotine withdrawal may increase the risk of POD [47, 48]. Since this might be especially relevant to patients with a high nicotine dependency, binary reporting of the smoking status may be inadequate.

The new DRD score was developed and validated in a cohort of orthopaedic and trauma surgery patients who are known to be at risk for POD due to multiple risk factors [49, 50]. The prevalence of POD in our study was 18.4% for patients > 65 years, which is comparable to previous findings. The overall incidence of delirium in hospitalized older adults was 23% according to a meta-analysis of 33 studies [2]. The incidence of POD varies depending on the type of surgery with ≥ 20% for major surgery, which includes interventions in orthopaedic and trauma surgery [2]. Due to the retrospective assessment of POD through documented 4AT scores, ICD-10 diagnosis, and chart review, underreporting is possible due to inappropriate documentation, especially for patients with

hypoactive delirium. Nonetheless, a chart-based method for identifying POD is validated and frequently used [51].

In this study, patients with a DRD score of 4 or higher were classified as at risk for POD. This applies for all patients > 65 years with an intake of at least two delirium risk-increasing drugs. For patients with less than two delirium risk-increasing drugs, depending on age, four points can only be reached if one or both additional risk factors (high anticholinergic burden and reduced kidney function) apply. For the predictive performance of the DRD score in the development and validation cohorts, sufficient AUC-values with 0.887 (95% CI 0.845–0.930) and 0.805 (95% CI 0.736–0.874) were obtained. Also calibration plots showed good calibration for both test cohorts (Fig. 1). The specificity and NPV were good in both development and validation cohort, meaning patients without risk will be stratified correctly. The sensitivity was good in the development cohort (83.3%), but lower in the validation cohort (63.3%), meaning some patients at risk could be missed. However, since the DRD score will be a first screening during PhMR and additional screening will take place on the ward, the achieved sensitivity was judged as acceptable. For patients identified at high risk for drug-related POD, pharmacists can consequently perform a medication review and state suggestions for drug therapy safety as an additional preventive measure to reduce the risk for POD.

Our study has several limitations. Since we performed a single centre study in a specific patient cohort of orthopaedic and trauma surgery patients, the generalizability of our findings is unknown and should be addressed in further studies. A number of important predictors for POD are not included in the DRD score, such as dementia, cognitive impairment, previously developed delirium, hearing and visual impairment, physical status, type of surgical procedure, and severity of illness [7, 25, 32, 33, 37, 46]. This is primarily due to its focus on implementation during PhMR, and we were thus limited to factors available at this time point. Although some patients with dementia receive anti-dementia drugs, we are aware that patients with unrecognized or untreated dementia will not be assessed. Patients who develop POD because of other, not drug-related risk factors might not be predicted through the DRD score. However, the focus of our new score includes delirium risk-increasing drugs and it could be a trigger for pharmaceutical advice with the aim to erase or minimize the risk for drug-related POD. Thus, the primary aim of the DRD score is to identify patients at risk for drug-related POD who may benefit from suggestions for drug therapy safety.

There is some overlap between our list of delirium risk-increasing drugs and drugs included in the ACB score. For receiving corresponding score points, at least two delirium risk-increasing drugs or an ACB score ≥ 3 are necessary. An ACB score ≥ 3 can either be reached for multiple drugs with a low to moderate anticholinergic effect or for single drugs with a high anticholinergic effect (e.g. tricyclic antidepressants or antimuscarinic agents for the treatment of overactive bladder). For drugs with high anticholinergic properties, which are also classified as delirium risk-increasing drugs, a double rating will only occur if other delirium risk-increasing drugs are taken in addition. Besides anticholinergic properties, delirium risk-increasing drugs have various other effects on the central nervous system or correlate with comorbidities associated with POD. Thus, cases with a double rating can be justified, and an additional risk for POD can be proposed due to multiple drug-related central nervous effects and associated comorbidities. Furthermore, for both risk factors no statistical multicollinearity was determined and the overlap was therefore not considered to be decisive.

We performed an internal validation in orthopaedic and trauma surgery patients. External validation in different surgical patient cohorts is necessary to estimate the score performance in other settings and determine the generalizability of the DRD score. However, as a strength, this study was performed with real-life data and considered the feasibility in clinical practice.

Conclusion

The new DRD score is a predictive risk score assessable during pharmacist-led medication reconciliation at hospital admission and is suitable for identifying patients at risk for drug-related POD. In addition to general preventive measures, specific preventive measures concerning drug therapy safety should be implemented for identified patients to reduce the risk for POD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05005-1.

Supplementary Material 1

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Author contributions

CG participated in the design of the study, was responsible for data acquisition and analysis and drafted the manuscript. TS, VS and KD were involved in the design of the study, served as experts in interprofessional discussions and result interpretation. UA was involved in scientific advice, statistical analysis and result interpretation. DS participated in the study design, interprofessional discussion of experts, data and result interpretation and review of the manuscript. All authors have reviewed and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of LMU University Hospital Munich (No. 23–0041) and complied with the Declaration of Helsinki. The Ethics Committee of LMU University Hospital Munich waived the requirement to obtain any informed consent due to the retrospective design of the study.

Guidelines
The 'Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis' (TRIPOD) reporting guideline [52] was followed during the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

6. Veröffentlichung II

Anticholinergic Exposure, Drug Dose and Postoperative Delirium: Comparison of Dose-Related and Non-Dose-Related Anticholinergic Burden Scores in a Retrospective Cohort Study of Older Orthopaedic and Trauma Surgery Patients

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ORIGINAL RESEARCH ARTICLE

Anticholinergic Exposure, Drug Dose and Postoperative Delirium: Comparison of Dose-Related and Non-Dose-Related Anticholinergic Burden Scores in a Retrospective Cohort Study of Older Orthopaedic and Trauma Surgery Patients

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Abstract

Purpose Postoperative delirium (POD) is a common complication in older adult patients after surgery. A patient's preoperative anticholinergic (AC) burden is a potentially modifiable risk factor for POD. As the influence of the drug dose remains unknown, we aimed to compare three AC burden scores in relation to POD, two of which were dose-related.

Methods This retrospective cohort study (03/22–10/22) included orthopaedic and trauma surgery patients > 65 years. POD was assessed using the four A's test (4AT), delirium diagnosis, and chart review. The AC burden was determined using the non-dose-related German Anticholinergic Burden score (GerACB), an extension of the dose-related Muscarinic Acetylcholinergic Receptor ANTagonist Exposure scale (extMARANTE), and the dose-related German Drug Burden Index (GerDBI). Multivariable logistic regression analysis determined the association between the preoperative AC burden and POD. Scores were compared using kappa statistics, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results POD was observed in 71 of 385 patients (18.4%). For all three scores, a high AC burden was significantly associated with POD after adjusting for age, sex, dementia, preoperative physical status, and number of prescribed drugs ($p < 0.001$). The overall agreement among the burden classifications was substantial (no POD: $\kappa = 0.645$, POD: $\kappa = 0.632$). The GerACB had the lowest sensitivity with 23.9% (extMARANTE: 42.3%, GerDBI: 40.8%), but the highest PPV with 48.6% (extMARANTE: 38.5%, GerDBI: 43.3%).

Conclusion Both dose-related and non-dose-related AC burden scores have limited sensitivity and modest PPV for screening a patient's medication for POD. However, given the additional effort required for dose consideration, the non-dose-related GerACB remains sufficient in clinical practice, with the lowest sensitivity but highest PPV.

1 Introduction

Postoperative delirium (POD) is the most common complication in hospitalised older adult patients undergoing surgery [1]. It is defined as a sudden change in attention, consciousness, and cognitive function that usually fluctuates in presence and severity [2]. The prevalence of POD depends on predisposing factors (e.g. age, frailty, comorbidities, cognitive impairment, and history of previous delirium) and precipitating risk factors (e.g. major surgery, infection, dehydration, pain, and medication use) and ranges from < 10% in medically well patients to 45–87% in intensive care units [3–5]. POD is associated with severe complications, such as increased mortality, longer hospital stays, cognitive decline, and the development of dementia [6, 7].

Although the pathophysiological mechanisms underlying POD are not yet fully understood, increasing evidence suggests an imbalance between neurotransmitters and inflammatory biomarkers [3, 4, 8]. Cholinergic dysfunction plays a key role, as the neurotransmitter acetylcholine mediates attention and memory processes through the muscarinic receptor subtype M1, which is predominantly located in the brain [9, 10]. Anticholinergic (AC) drugs inhibit central and peripheral cholinergic transmission, and their effects

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Extended author information available on the last page of the article

Key Points

The association between preoperative anticholinergic burden and postoperative delirium has been reported inconsistently, and the influence of drug dose is unknown.

For both dose-related and non-dose-related anticholinergic burden scores, a high burden was significantly associated with postoperative delirium, and the overall agreement between the burden classifications was substantial.

Compared with the dose-related scores, the simple German anticholinergic burden score had the lowest sensitivity but highest positive predictive value and remains a sufficient tool for screening a patient's medication with regard to postoperative delirium.

on central cholinergic activity can thus lead to cognitive impairment and an increased risk of delirium [11, 12]. This is especially relevant in older adult patients, since they are more susceptible to AC effects due to increased AC sensitivity and changes in pharmacokinetics [13]. While some drugs are used specifically because of their AC effects (such as urinary antispasmodics), others present AC adverse effects unrelated to their intended therapeutic effect (e.g. some antipsychotics).

To quantify the cumulative AC effect of a medication (often referred to as AC burden), over 20 scores have been established in the past. The published scores differ in the number and selection of included drugs, the classification of potency properties, and the method of calculating the cumulative burden [14, 15]. For the majority of the scores, drugs are assigned potency properties ranging from zero (no effect) to three (high effect), and the cumulative medication burden is added up. To our knowledge, only one scale considers both anticholinergic potency and drug dose, which is the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure scale (MARANTE) [16]. Another score that also differs from most AC burden scores is the Drug Burden Index (DBI) [17], which takes the minimal effective dose of AC and sedative drugs into account. However, whether the dose needs to be considered in addition to the general AC potency of a drug regarding clinical outcomes is still unclear.

Numerous studies have examined the associations between AC burden and clinical outcomes, such as POD [18–20], reduced cognition [11], mortality [21], and falls [22]. In a previous study, we found that the AC burden of the admission medication was a significant risk factor for POD, and this has been included in a newly developed predictive risk score for POD developed by our group [23]. Overall, AC burden scales vary in their association with reduced cognition and delirium, and contradictory results have been reported [14, 15, 24]. However, a higher DBI was associated with decreased cognition and delirium, and seemed to be more reliable when predicting AC adverse events related to cognition compared with AC burden scores without dose consideration [25, 26]. Furthermore, a higher cumulative dose-responsive AC use was associated with an increased risk for cognitive decline, which is again a major risk factor for POD [3, 11]. In addition, individual drugs, such as oxybutynin, show a dose–response risk for delirium [27]. This leads to the question of whether the dose of AC drugs should be considered when screening preoperative medication for POD. However, in studies comparing a variety of established AC burden scores and their associations with POD, dose-related measures such as the MARANTE scale or the DBI are absent [18]. Thus, evidence on the performance of dose-related compared with non-dose-related AC burden scores in relation to clinical outcomes, especially POD, is limited [12, 14].

Calculating dose-related AC burden scores can be complex and time consuming. Furthermore, the necessary dose or intake frequency is often missing or incorrectly documented at hospital admission [28]. As a patient's AC burden is a potential modifiable risk factor for POD, a dose-dependent relationship would suggest that reducing the dose of AC drugs could be a preventive measure for risk reduction, apart from discontinuing the drug. As the MARANTE scale is the only AC burden scale linking potency with dose, and a non-dose-related AC burden score and a dose-related DBI exist for Germany, the comparison of these three scores was of special interest. Therefore, this study aimed to compare the German AC burden score, the MARANTE scale, and the German DBI for their association with POD and to evaluate whether dose-related scores are more suitable than a simple AC burden score for screening a patient's medication for POD.

2 Methods

2.1 Study Design and Setting

A single-centre cohort study at LMU University Hospital Munich, Germany was conducted from March 2022 to October 2022 with the primary aim of developing a drug-based risk score for POD [23]. The study was approved by the Ethics Committee of LMU University Hospital Munich (no. 23-0041). This is a secondary sub-analysis that included inpatients over 65 years of age who underwent surgical intervention in orthopaedics or trauma surgery and who received pharmacist-led medication reconciliation at hospital admission. In the primary study [23], patients with preoperative

delirium and delirium due to alcohol withdrawal, as indicated in patient records, were excluded. This sub-analysis further excluded patients with missing information on drug dose.

Patients from three orthopaedic and trauma surgery wards were included, which all participated in the project 'gertrud – age-appropriate proactive health care' with a focus on reducing postoperative complications in older adult patients, specifically delirium [29]. Therefore, ward staff were especially trained for delirium awareness, and trained nurses assessed delirium two to three times a day using the four A's test (4AT) [30]. The 4AT considers alertness, attention assessment (through the month backwards test), the four-item Abbreviated Mental Test (AMT4: age, date of birth, current place and year), and evidence for acute change or fluctuating course. For patients with a 4AT ≥ 4, physicians checked for the presence of delirium and, if present, documented a diagnosis code according to the International Classification of Diseases, 10th Revision (ICD-10).

Pharmacist-led medication reconciliation is routinely performed at admission for all surgical patients from Monday to Friday. This results in a detailed medication history of drugs (prescribed, over-the-counter, and phytopharmaceuticals), including long-term and on-demand medication, which is saved as admission medication in the electronic medication record Meona® (Mesalvo GmbH Freiburg, Germany).

2.2 Data Collection

Drugs and dosages of the admission medications were retrieved from Meona®. Sociodemographic and laboratory data as well as disease-related information of the patients (diagnoses coded according to ICD-10, 4AT scores, chart entries, and data from the preoperative anaesthesia assessment) were collected from the electronic patient information system (i.s.h.med®, Cerner Corporation, North Kansas City, USA). Dementia status was recorded according to ICD-10 codes (F00.-*, F01, F02.-*, F03, F05.1), chart review (keyword: dementia), or the use of anti-dementia drugs. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [ml/min/1.73 m^2] [31].

2.3 Retrospective Assessment of Postoperative Delirium

For each inpatient stay, POD was assessed up to 7 days post-surgery according to the documented ICD-10 codes (F05.0, F05.1, F05.8, and F05.9). Additionally, as validated in previous studies [32, 33], a subsequent chart review was performed (keywords: delirious, confused, disoriented, disturbed attention, hallucination, restless, and agitated). POD was considered to be present if either an appropriate ICD-10 code was documented or the chart review clearly indicated the development of POD. The assessment occurred independently of the knowledge of AC burden scores. After the initial assessment by a pharmacist, a physician confirmed the final POD rating.

2.4 Extension of the MARANTE Scale

The authors of the original MARANTE scale published dose ranges for 41 AC drugs and suggested the completion of additional country-specific or newly developed AC drugs [16]. Thus, we defined the dose values (minimal effective value, main dose, and maximal effective value) for all the remaining AC drugs determined using the GerACB score in our patient cohort. To adapt the potency values, we assigned ACB 1 as 'low potency' (potency value of 1) and ACB 2 and 3 as 'high potency' (potency value of 2).

Following the methodological approach of the original MARANTE scale, we retrieved dosage information from multiple international sources and invited an expert panel to rate dosage concepts. We determined the main indications according to the World Health Organization (WHO) Collaboration Centre for Drug Statistics Methodology [34]. As international reference sources for dosage information for the main indication, we consulted UpToDate® [35], the British National Formulary [36], and the Geriatric Dosage Handbook [37]. Second, we retrieved information from the German Summary of Product Characteristics (SmPC) [38].

The expert panel included three experts with expertise and experience in drug use in older adult patients (one clinical geriatrician and two clinical pharmacists with long-term experience in drug information). We conducted two rounds. First, the experts filled in the remaining dosage values (minimal effective value, main dose, and maximal effective value) for the remaining AC drugs based on the reference sources, their clinical experience, and the available dosage forms. Once the rated dosage values were collected, they were evaluated for consensus. Consensus was reached when at least two experts rated an identical dosage value. For drugs for which this was not possible, we conducted a second round in which the experts received anonymous ratings from the first round and were asked to revise their ratings. After the second round, all dosage concepts were determined through consensus.

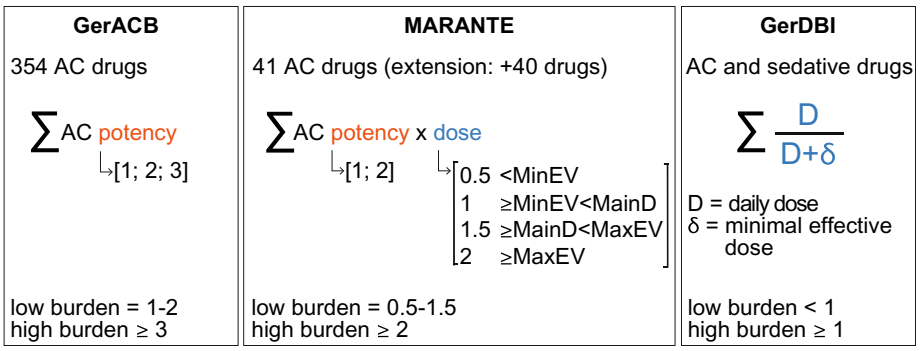

Fig. 1 Composition of the scores for assessment of the AC exposure. For each listed drug, an individual burden value is calculated depending on the assigned potency (GerACB [39]), potency and dose (MARANTE [16]), or only dose (GerDBI). To determine a patient's overall burden, individual burden values are summed up. *AC* anticholinergic, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *MainD* maintenance dose, *MARANTE* Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *MaxEV* maximal effective value, *MinEV* minimal effective value

2.5 Assessment of AC Exposure

For each patient's admission medication, AC exposure was calculated according to the following three scores/equations:

1. The German Anticholinergic Burden score (GerACB) [39];
2. The Muscarinic Acetylcholinergic Receptor ANTagonist Exposure scale (MARANTE) [16];
3. The German Drug Burden Index (GerDBI).

The GerACB assigns values from one to three to drugs based on their AC potency. Both the MARANTE scale and the GerDBI are equations that consider the dosage. The MARANTE scale links dose and potency, while the GerDBI does not consider potency but additionally includes sedative drugs. Fig. 1 shows an overview of the score calculations according to these three scores. The GerDBI is based on the Drug Burden Index by Hilmer et al. [17, 40] and includes drugs available in Germany. It was developed as part of the 'COFRAIL' project [41] (funding code 01VSF17053), and details will be published elsewhere.

For the calculation of dose-related equations, the average daily dosage was needed. On-demand medication was only rated if the intake frequency could be obtained from the pharmacist-led medication reconciliation; otherwise, drugs were not rated. Cumulative AC exposure was reported either as a continuous burden value or as a categorical burden (no burden, low burden, or high burden) to allow comparability of the scores/equations. For each score, established burden classifications were used for no burden, low burden, and high burden: GerACB (0, 1–2, ≥ 3), MARANTE (0, 0.5–1.5, ≥ 2) and GerDBI (0, > 0 < 1, ≥ 1) [16, 39, 40].

2.6 Statistical Analysis

Descriptive statistics are reported as means ± standard deviation (SD), median and interquartile range (IQR), or as frequencies with percentages. Groups were compared using Mann–Whitney *U* test or chi-squared test. Pairwise or overall agreement of AC burden classifications between all three scores was assessed using kappa statistics, and the agreement classification followed Landis and Koch [42]. Associations of AC burden (estimated through the GerACB, MARANTE, and GerDBI) with POD were determined via multivariable logistic regression analyses. For adjustment of co-variables, significant variables ($p < 0.05$) from univariable analysis were added to a stepwise forward multivariable logistic regression model. Sex was added as a forced-in variable. Multicollinearity of co-variables was determined through a correlation matrix. The performance of the model was evaluated by the area under the curve (AUC) of receiver operating characteristic (ROC) analysis. To estimate the score performance, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained in an unadjusted analysis. All calculations were performed with SPSS Statistics® version 29.0 (IBM Corp., Armonk, NY, USA). Illustrations were created using Adobe Illustrator® version 27.0 (San Jose, CA, USA). *P* values < 0.05 were considered statistically significant.

The sample size was calculated considering six variables included in the multivariable analysis, ten outcome events per variable [43], and an estimated POD prevalence of 20% [3], for which a minimum of 300 patients were estimated.

3 Results

3.1 Extension of the MARANTE Scale

Among the 40 missing AC drugs taken by the study cohort, 30 dosage ranges could be determined by consensus in the first round. Ten drugs underwent a second round, after which all dosage ranges were obtained by consensus. A full list of the extended dosage values is shown in the Online Resource 1, Table 1. The original MARANTE scale complemented with the extended version will be referred to as the extended MARANTE scale (extMARANTE).

3.2 Patient Characteristics, Preoperative AC and Sedative Drug Exposure and Score Interrater Reliability

Of the 546 patients initially included in the primary study [23], 385 patients over 65 years of age were included in this secondary sub-analysis (n = 161 patients 65 years of age and under were excluded). Throughout the study period, 71 patients (18.4%) developed POD. Patients with POD were significantly older and had a higher prevalence of dementia, a lower body mass index (BMI), and a higher American Society of Anesthesiologists (ASA) physical status than patients without POD (Table 1). In addition, POD was associated with reduced kidney function at admission and a higher total number of drugs. No patients had missing information on drug dose. The frequency of on-demand medication was unclear for 17 drugs (GerDBI) and 11 drugs (extMARANTE); these drugs were excluded from further analysis. According to the GerACB, extMARANTE, and GerDBI, patients with POD had a higher intake of AC and sedative drugs and the median scores were significantly increased. No sex differences were found.

Fig. 2 shows the distribution of the burden categories (no, low, and high burden) for AC and sedative drug exposure determined through the GerACB, extMARANTE, and GerDBI for patients with and without POD. Overall, the interrater reliability between the burden classifications of all three scores determined through Fleiss' kappa resulted in substantial agreement for patients with and without POD (Table 2). Pairwise interrater reliability calculated via Cohen's kappa indicated substantial or moderate agreement for burden classifications depending on the compared scores and patient group. The lowest agreement was determined between the GerACB and the GerDBI for patients with POD, and the highest agreement was achieved between the GerACB and the extMARANTE among patients without POD.

Table 1 Patient characteristics and AC and sedative drug exposure for patients with and without POD

Characteristic	No POD n = 314 (81.6%)	POD n = 71 (18.4%)	p
Age (years)	78.5 (72–83)	85 (79–90)	< 0.001[a]
Female sex	187 (59.6)	40 (56.3)	0.619[b]
Dementia	13 (4.1)	30 (42.3)	< 0.001[b]
BMI (kg/m^2)	25 (22–28)	23 (21–26)	0.006[a]
ASA physical status			
1–2	113 (36)	4 (5.6)	< 0.001[b]
3–4	201 (64.0)	67 (94.4)	
eGFR at admission (ml/min/1.73 m^2)	74 (58–85)	55 (36–79)	< 0.001[a]
Total number of drugs per patient	4 (2–7)	7 (5–11)	< 0.001[a]
Patients with AC drugs included in the GerACB/extMARANTE	102 (32.5)	48 (67.6)	< 0.001[b]
Patients with AC and sedative drugs included in the GerDBI	127 (40.4)	55 (77.5)	< 0.001[b]
Thereof patients with sedative drugs included in the GerDBI	25 (8.0)	11 (15.5)	0.05[b]
GerACB (score points)	0 (0–1)	1 (0–2)	< 0.001[a]
extMARANTE (score points)	0 (0–1)	1.5 (0–3)	< 0.001[a]
GerDBI (score points)	0 (0–0.5)	0.7 (0.3–1.5)	< 0.001[a]

Numbers are expressed as n (%) or as median (interquartile range)

AC anticholinergic, *ASA* American Society of Anesthesiologists, *BMI* Body Mass Index, *eGFR* estimated glomerular filtration rate, *extMARANTE* extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *POD* postoperative delirium

[a]Mann–Whitney U test comparing patients with and without POD

[b]Chi-squared test comparing patients with and without POD

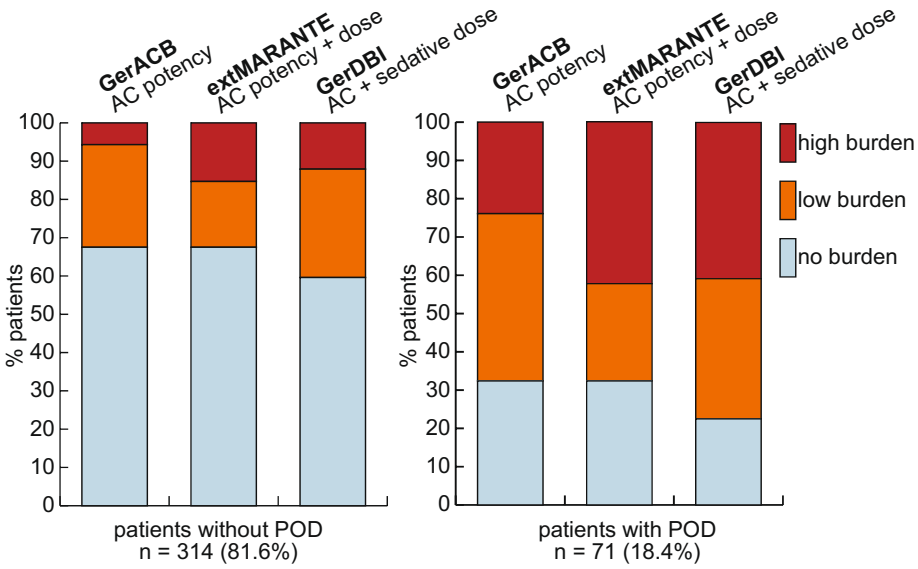

Fig. 2 Distribution of the burden categories for patients with and without POD. Classification of AC and sedative burden categories: low burden (GerACB 1–2; extMARANTE 0.5–1.5; GerDBI > 0 < 1) and high burden (GerACB ≥ 3; extMARANTE ≥ 2; GerDBI ≥ 1). *AC* anticholinergic, *extMARANTE* extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *POD* postoperative delirium

3.3 Association of Preoperative AC and Sedative Drug Exposure with POD and Score Performances

The results of the multivariable analysis of the categorical AC burden classifications and POD adjusted for the co-variables age, sex, dementia status, ASA physical status, and total number of drugs are shown in Table 3. For all three scores, a high burden was significantly associated with the development of POD compared to no burden, while a low burden was not significant. Testing for multicollinearity of variables indicated a low correlation (< 0.8) [44]. For the multivariable models, the following AUC values were obtained depending on the AC burden scores included: GerACB (0.902; 95% confidence interval [CI] 0.865–0.938), extMARANTE (0.902; 95% CI 0.865–0.939), and GerDBI (0.907; 95% CI 0.874–0.941).

The score performances were compared on the basis of sensitivity, specificity, PPV, and NPV (Table 4). The sensitivity was lowest for the GerACB and highest for the extMARANTE, whereas the PPV was highest for the GerACB and lowest for the extMARANTE.

4 Discussion

In this retrospective study, which included orthopaedic and trauma surgery patients over 65 years of age, we found a significant association between a high preoperative AC burden and the development of POD, as assessed by

Table 2 Pairwise and overall interrater reliability between the burden classifications (no, low, or high burden) for patients with and without POD

	No POD			POD		
	GerACB	extMARANTE	GerDBI	GerACB	extMARANTE	GerDBI
extMARANTE	κ = 0.779 p < 0.001 (95% CI 0.749-0.808)	-	-	κ = 0.732 p < 0.001 (95% CI 0.670-0.794)	-	-
GerDBI	κ = 0.591 p < 0.001 (95% CI 0.552-0.631)	κ = 0.579 p < 0.001 (95%CI 0.541-0.618)	-	κ = 0.516 p < 0.001 (95% CI 0.438-0.594)	κ = 0.659 p < 0.001 (95% CI 0.589-0.730)	-
Overall Agreement	κ = 0.645, p < 0.001 (95% CI 0.595-0.695)			κ = 0.632, p < 0.001 (95% CI 0.537-0.727)		

Agreement interpretation according to Landis and Koch [42]: substantial 0.61-0.8, moderate 0.41-0.6
CI confidence interval, *extMARANTE* extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *POD* postoperative delirium

Table 3 Multivariable regression analysis of the burden classifications of the GerACB, extMARANTE, and GerDBI for the outcome POD

Score	Multivariable analysis	
	OR (95% CI)	*p*
GerACB		
No burden	*Reference*	
Low burden	2.14 (0.98–4.66)	0.057
High burden	7.30 (2.50–21.27)	< 0.001
extMARANTE		
No burden	*Reference*	
Low burden	1.43 (0.57–3.57)	0.441
High burden	5.16 (2.19–12.15)	< 0.001
GerDBI		
No burden	*Reference*	
Low burden	1.97 (0.84–4.63)	0.121
High burden	6.50 (2.38–17.77)	< 0.001

Multivariable analysis adjusted for age, sex, dementia, American Society of Anesthesiologists physical status, and total number of drugs

Classification of AC and sedative burden categories: low burden (GerACB 1–2; extMARANTE 0.5–1.5; GerDBI > 0 < 1) and high burden (GerACB ≥ 3; extMARANTE ≥ 2; GerDBI ≥ 1)

AC anticholinergic, *CI* confidence interval, e*xtMARANTE* extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *POD* postoperative delirium

dose-related and non-dose-related AC burden scores. The overall agreement between the burden classifications of the three scores was substantial. The simple GerACB identified fewer patients with a high AC burden than the dose-related extMARANTE and GerDBI. Although the sensitivity of the GerACB was the lowest, the PPV was the highest.

Table 4 Performance of the GerACB, extMARANTE, and GerDBI with a high burden and the outcome POD

	GerACB	extMARANTE	GerDBI
Patients with a high AC and sedative burden	35 (9.1)	78 (20.3)	67 (17.4)
Sensitivity (%)	23.9	42.3	40.8
Specificity (%)	94.2	84.7	87.9
PPV (%)	48.6	38.5	43.3
NPV (%)	84.5	86.6	86.8

Numbers are expressed as *n* (%) or percentages

n = 385 patients, POD prevalence 18.4%

AC anticholinergic, e*xtMARANTE* extended Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale, *GerACB* German Anticholinergic Burden Score, *GerDBI* German Drug Burden Index, *NPV* negative predictive value, *POD* postoperative delirium, *PPV* positive predictive value

Considering the AC dose through the extMARANTE did not result in a substantial advantage compared with the GerACB. The GerDBI might be a promising tool because it also includes dose and sedative drugs. To summarize, all three scores were suitable for screening a patient's medication for POD, although all had only moderate sensitivity. In general, their high specificity allows ruling out patients with a low risk of POD. As dose consideration requires additional effort, the simple GerACB score remains sufficient for easy estimation of a patient's AC burden, which is a potentially modifiable risk factor for POD.

The aetiology of POD is multi-factorial, with drugs representing only one of the numerous risk factors. According to the neurotransmitter hypothesis, disturbances in neurotransmitter systems, particularly the cholinergic system, play a central role in the development of delirium [4]. AC drugs can reduce the cholinergic inhibition of microglia, which increases neuroinflammation. This can consequently lead to delirium and neurodegeneration, which are associated with long-term cognitive decline [45]. A positive association between non-dose related AC burden scores and delirium has also been reported by Herrmann et al. (1470 surgical patients ≥ 70 years) and Lisibach et al. (26,302 hospitalised patients ≥ 65 years) [18, 19]. Other studies have also reported an association of a high exposure of the drug-related DBI with delirium (721 patients with dementia) [46]. To the best of our knowledge, no study has yet investigated the association of the MARANTE scale with delirium. In contrast, no or inconsistent association between the preoperative non-dose related AC burden and delirium has been reported by other studies: Heinrich et al. (837 older adult surgical patients) and Pasina et al. (447 older hospitalised patients) [20, 24]. Heinrich et al. excluded patients with cognitive impairment. As AC drug use is associated with reduced cognitive function in older adult patients [11] and cognitive impairment is a major risk factor for delirium [3], the exclusion of these patients might explain the missing association of AC burden with POD. Another possible reason for the inconclusive association could be the use of different AC burden scores since there is no universally accepted version. The use of different AC burden scores could also account for the varying AC drug intake observed. In studies investigating the association between preoperative AC exposure and delirium, the reported prevalence of patients taking AC drugs varies widely, ranging from 7.2–8.9% [19] and 7.2–23.8% [20] to 79% [24]. In addition to the use of different AC burden scores, international differences in prescribing practices and varying levels of completeness of medication data have an impact on the observed AC drug intake.

As AC adverse effects are presumed to be dose-related, a dose-dependent AC risk for POD is a plausible concept. Other studies have investigated the association between the dose-dependent MARANTE scale and clinical outcomes.

Dinh et al. found that AC burden scores (MARANTE, GerDBI, and non-dose-related scores) were no significant predictors of falls [22]. However, a high exposure of the MARANTE scale was associated with an increased risk of mortality and hospitalisation [47]. In our study, high AC burden and POD were significantly associated for both dose-related and non-dose-related scores. After extending the original MARANTE scale, the extMARANTE included the same AC drugs as the GerACB, but additionally considered the drug dose (low, moderate, high, or very high). The agreement between the burden classifications of the GerACB and extMARANTE was substantial. Overall, the extMARANTE rated more patients with a high burden than the GerACB. This resulted in a higher sensitivity of 42.3% versus 23.9% (GerACB) but also in a lower PPV of 38.5% versus 48.6% (GerACB). To summarize, although AC drug use was associated with POD, adjusting for dose still resulted in a similar burden classification and did not substantially improve the clinical usefulness of the score in predicting POD.

Compared with the AC burden scores, the GerDBI additionally included sedative drugs. Overall, more patients with POD took sedative drugs than patients without POD, although the difference was not significant. The inclusion of sedative drugs might explain the lower agreement among the burden classifications for the GerACB and the GerDBI. Considering the sensitivity and PPV, the GerDBI performed well compared with the GerACB and extMARANTE. To summarize, the inclusion of sedative drugs in the GerDBI might bring an advantage when screening a patient's medication with regard to POD.

To the best of our knowledge, this is the first study to examine the association between dose-related AC burden scores and the outcome POD. In addition to other studies that investigated the association between the MARANTE scale and clinical outcomes, we expanded the original MARANTE scale to include AC drugs relevant to our German patient cohort. As a strength of our study, we had a reliable source for calculating the average daily dose since the medication and drug doses were retrieved on the basis of pharmacist-led medication reconciliation at hospital admission, which also included over the counter (OTC) drugs and intake frequencies of on-demand drugs.

Our study had several limitations. This was a retrospective, single-centre study, and the generalizability of our findings is limited. We are aware that, for POD in particular, AC drugs acting on the central nervous system play a determining role. The GerACB does not have a specific focus on central nervous acting drugs in comparison to other AC burden scores (such as the AC cognitive burden scale [48]). However, the score is well established in Germany, the overall quality is rated high [14], and an association with POD has also been reported previously [18]. By using a preliminary version of the GerDBI, which has not yet been published, it cannot be ruled out that there may be minimal changes in the GerDBI performance when using the final version. We did not consider drugs administered during the inpatient stay, including anaesthesia relevant drugs, but solely assessed long-term medication at admission. This provides insight into AC exposure as a predisposing risk factor rather than a triggering risk factor for POD. In addition to the theoretical AC burden determined through medication-based scores, actual patient-relevant AC symptoms, as depicted by a neuropsychological assessment battery [49], could account for interindividual differences. We did not consider this aspect in the assessment of AC burden, but merely focused on the theoretical burden based on the patient's medication. During the study period of this retrospective study, geriatric screening and frailty assessments were not consistently performed for all included patients. Instead, to account for the patient's physical status, we included the ASA physical status, as this was assessed for all patients undergoing surgery. An important limitation in studies with the endpoint POD is the sensitivity of the outcome assessment. Underrating is a possible source of bias. To address this, we chose a study setting with established POD screening and performed a chart review, which is a validated method that increases the reliability of the POD outcome [32]. The prevalence of POD in our cohort (18.7%) was comparable with that in other studies [4]. This study included orthopaedic and trauma surgery patients. Further validation studies are needed to investigate patient cohorts undergoing other types of surgery or hospitalised with acute medical conditions.

An important aspect of the use of medication scores is their usability in daily clinical practice. Online tools or calculators have been developed for the GerACB and DBI [50, 51], which allow easy estimation of the AC burden but also require active input of the patient's medication. To ensure practicability, an automated calculation of the AC burden integrated into electronic prescribing software is necessary, especially for dose-related scores. This would increase the awareness of physicians and pharmacists regarding the use of AC drugs, as they do not require active entry. Until automated calculations are established, non-dose-related scores, such as the GerACB, are the most practical and reliable option. In addition to practicability, feasible interventions should be developed and implemented as part of a systematic POD prevention strategy for patients with a high AC burden. Similar clinical decision pathways have been reported in previous studies [52]. In addition to the admission medication, the influence of intraoperative AC or sedative drugs on the development of POD should be further investigated.

5 Conclusion

To summarize, we found a significant association between a high AC burden and POD, as determined through both dose-related and non-dose-related scores. All three scores showed only moderate sensitivity. By comparing the scores, we determined substantial agreement among the burden classifications. The inclusion of the AC drug dose (extMARANTE) did not result in a substantial advantage; however, considering dose and sedative drugs as done by the GerDBI might be promising. Overall, we found the non-dose-related GerACB to be sufficient for easy screening of a patient's medication for POD.

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Declarations

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Availability of Data and Material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval The study was approved by the Ethics Committee of LMU University Hospital Munich (No. 23-0041) and complied with the Declaration of Helsinki.

Consent to Participate The Ethics Committee of LMU University Hospital Munich waived the requirement to obtain any informed consent due to the retrospective design of the study.

Consent for Publication Not applicable

Code Availability Not applicable

Author Contributions The authors contributed to the paper as follows. Study conception: C.G., T.S., K.D., U.A., and D.S. Expert committee for anticholinergic dose values: C.R., V.S., and D.S. Data collection: C.G. and T.S. Data analysis: C.G., U.A., and D.S. Manuscript – original draft: C.G. All authors have read and approved the final version of the manuscript and agree to be accountable for the work.

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Erklärung zur Übereinstimmung der gebundenen Ausgabe der Dissertation mit der elektronischen Fassung

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Hiermit erkläre ich, dass die elektronische Version der eingereichten Dissertation mit dem Titel:

Arzneimittel bei stationärer Aufnahme als prädiktiver Risikofaktor für postoperatives Delir

in Inhalt und Formatierung mit den gedruckten und gebundenen Exemplaren übereinstimmt.

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