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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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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.

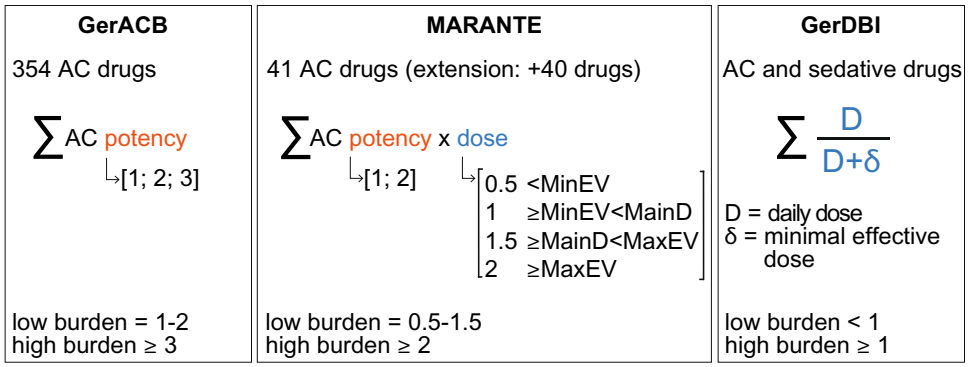

Fig. 1 Composition of the scores for assessment of the AC exposure. For each listed drug, an individual burden value is calculated depending on the assigned potency (GerACB [39]), potency and dose (MARANTE [16]), or only dose (GerDBI). To determine a patient's overall burden, individual burden values 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, e*xtMARANTE* 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

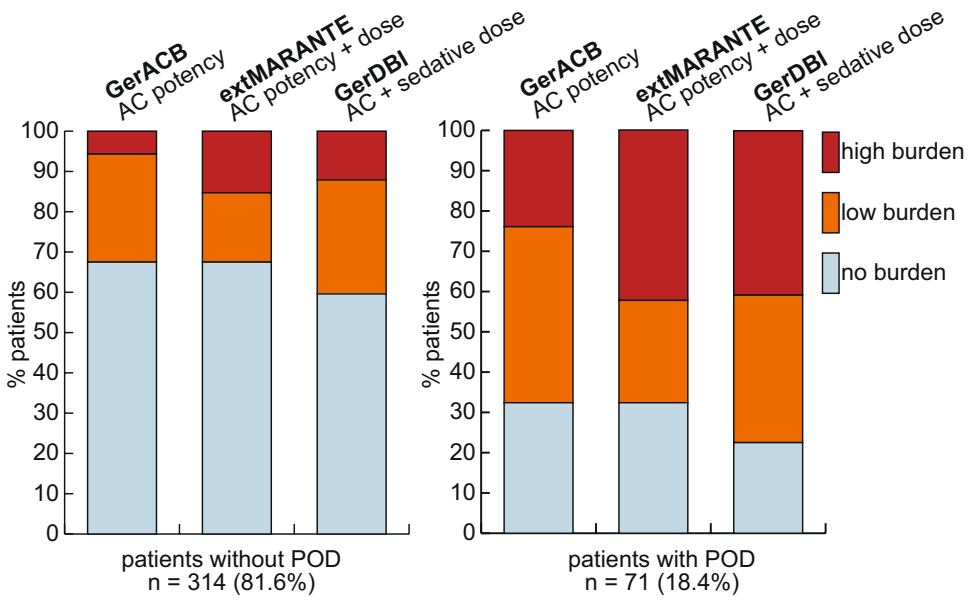

Fig. 2 Distribution of the burden categories for patients with and without POD. Classification of AC and sedative burden categories: low burden (GerACB 1–2; extMARANTE 0.5–1.5; GerDBI > 0 < 1) and high burden (GerACB ≥ 3; extMARANTE ≥ 2; GerDBI ≥ 1). *AC* anticholinergic, e*xtMARANTE* extended Muscarinic 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, e*xtMARANTE* 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

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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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