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ORIGINAL ARTICLE

Evaluation of the association of anticholinergic burden and delirium in older hospitalised patients – A cohort study comparing 19 anticholinergic burden scales

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Aims: A recent review identified 19 anticholinergic burden scales (ABSs) but no study has yet compared the impact of all 19 ABSs on delirium. We evaluated whether a high anticholinergic burden as classified by each ABS is associated with incident delirium.

Method: We performed a retrospective cohort study in a Swiss tertiary teaching hospital using data from 2015–2018. Included were patients aged ≥65, hospitalised ≥48 hours with no stay >24 hours in intensive care. Delirium was defined twofold: (i) ICD-10 or CAM and (ii) ICD-10 or CAM or DOSS. Patients' cumulative anticholinergic burden score, calculated within 24 hours after admission, was classified using a binary (<3: low, ≥3: high burden) and a categorical approach (0: no, 0.5–3: low, ≥3: high burden). Association was analysed using multivariable logistic regression.

Results: Over 25 000 patients (mean age 77.9 ± 7.6 years) were included. Of these, (i) 864 (3.3%) and (ii) 2770 (11.0%) developed delirium. Depending on the evaluated ABS, 4–63% of the patients were exposed to at least one anticholinergic drug. Out of 19 ABSs, (i) 14 and (ii) 16 showed a significant association with the outcomes. A patient with a high anticholinergic burden score had odds ratios (ORs) of 1.21 (95% confidence interval [CI]: 1.03–1.42) to 2.63 (95% CI: 2.28–3.03) for incident delirium compared to those with low or no burden.

Conclusion: A high anticholinergic burden within 24 hours after admission was significantly associated with incident delirium. Although prospective studies need to confirm these results, discontinuing or substituting drugs with a score of ≥3 at admission might be a targeted intervention to reduce incident delirium.

KEYWORDS
anticholinergic burden, delirium during hospitalisation, DOSS, older patients

The authors confirm that the Principal Investigator for this paper is Chantal Csajka, and that Dr. Csajka had direct clinical responsibility for patients.

1 | INTRODUCTION

Delirium is defined as an acute mental state of confusion caused by a dysregulation of baseline neuronal activity, with incidence rates of delirium arising during hospitalisation ranging from 6% to 56%.[1] It is a potentially preventable source of morbidity and mortality in older hospitalised patients, leading to longer and costlier hospitalisations.[2] Though the pathophysiology is not yet fully understood, the neurotransmitter and neuroinflammation hypothesis suggest a misbalance of neurotransmitters or cytokines to be the cause.[3] One of these neurotransmitters is acetylcholine. A deficiency of acetylcholine can be induced by the intake of drugs with anticholinergic (ACH) properties. These drugs act on the muscarinic receptors in the central and peripheral nervous system and inhibit ACH-mediated responses by competitive binding.[4] The muscarinic receptor subtype M1 in particular appears to be important in relation to delirium, as it is a crucial receptor for cognitive and memory learning and is predominantly found in the brain.[5,6] While some medications are used on purpose for their ACH action, others have ACH activity unrelated to their mechanism of action. Nearly half of the older people, who are particularly susceptible to adverse drug events (ADEs) due to changes in pharmacokinetics and pharmacodynamics or ACH hypersensitivity, are taking at least one drug with ACH properties.[4,7]

Over the past decades, numerous drug lists, called anticholinergic burden scales (ABSs), have been developed usually assigning a number from one (low) to three (high) to each substance. The cumulative ACH burden for a patient is calculated by adding the scores of each substance prescribed. The resulting score should help identify patients at high risk for ACH-related ADEs for possible interventions.

In a recent systematic review,[8] we identified 19 ABS from different countries and with varying qualities.[9–27] Newer ABSs were developed by reviewing prior published scales,[11,16,20,21,23] whereas other ABSs are derived from a serum ACH activity assay (SAA)[15,22] or computational receptor binding affinities.[27] Most of the ABSs also considered expert committee opinions.

However, in particular newer ABSs lack validation in clinical settings and others show conflicting results regarding the association with delirium. To our knowledge, no study has yet investigated all 19 ABSs with delirium using the same clinical setting. Hence, in this study, we aim to compare all published ABSs and evaluate their association with delirium developed in older patients during hospitalisation.

What is already known about this subject

- Drugs with anticholinergic properties are frequently used in older hospitalised patients despite their potential for adverse effects, such as delirium.
- Over the past four decades, 19 so-called anticholinergic burden scales (ABSs) have been developed in order to quantify the overall cumulative anticholinergic drug burden within a patient.
- Previous studies have evaluated the association of the cumulative anticholinergic drug burden and delirium but their results are inconclusive, none has compared all published ABSs simultaneously and most reports have looked at specific populations.

What this study adds

- This is the first study to our knowledge to evaluate the association of all 19 ABSs with incident delirium in older hospitalised patients.
- Newer, high-quality ABSs seem to be the best suited for clinical use when investigating the outcome delirium.
- A cumulative anticholinergic burden score of ≥3 points within the first 24 hours of admission is associated with delirium development during hospitalisation.

2 | METHOD

2.1 | Study design and setting

We performed a retrospective cohort study of patients hospitalised between January 2015 and December 2018 in a Swiss tertiary teaching hospital. We derived our data set from electronic health records (EHR), i.e., data routinely prospectively collected during hospitalisation. This study was undertaken per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[28]

2.2 | Ethics approval

This study was approved by the Swiss ethics review committee (EKNZ Project ID: 2018–01000). A similar study investigating the association of the ACH burden with in-hospital mortality and length of stay was published using the same data set.[29]

2.3 | Participants

We included patients aged 65 years and older, who had been hospitalised for at least 48 hours. Patients presenting delirium within the first 24 hours of hospitalisation or those with delirium related to substance abuse (defined by the International Classification of Disease 10 [ICD-10] codes F10.4, F11.4, F12.4, F13.4, F14.4, F15.4, F16.4, F17.4, F18.4 and F19.4) were excluded. We further excluded patients who stayed on an intensive care unit (ICU) for more than 24 hours, because the ICU staff did not order electronically.

2.4 | Data collection

Data were extracted for each patient from the hospital's clinical information system, such as demographic characteristics, comorbidities, laboratory values, medication intake and nurse assessments (ergebnisorientiertes PflegeAssessment Acute Care [ePA-AC][30]). Comorbidities were identified according to the Charlson comorbidity index based on the ICD-10 codes assigned at discharge using the R package *{comorbidity}*.[31] The following comorbidities were additionally grouped: cancer and metastatic cancer (cancer), mild to severe liver disease (liver disease), and diabetes with and without chronic complications (diabetes). Coded comorbidities were carried forward in case of repeated hospitalisations because we considered these to be chronic conditions.

The nurse assessment tool ePA-AC[30] is a systematic observational tool assessing information on cognition, care, mobility and nutritional status of patients. It entails the self-care index (SPI), the Braden score, the nutrition score and binary variables for risk of falling and the risk of pneumonia. An SPI score of 32 points or more means that patients can take care of themselves, a Braden score of 12 points or less is associated with a high risk for the development of decubitus, a nutrition deficiency score with three or more points representing malnutrition. In this Swiss tertiary teaching hospital, the ePA-AC is performed by nurses at admission and then every other day.

We only considered variables with more than 20% available data and generated the potential category '*missing*' for categorical or binary variables. The following variables contained missing values (%) in the primary resp. secondary analysis: aspartate transaminase (ASAT) (27.4% resp. 28.2%), alanine transaminase (ALAT) (72.8% resp. 72.9%), glomerular filtration rate (GFR) (11.02% resp. 11.4%), creatinine (10.8% resp. 11.8%), potassium (11.1% resp. 11.4%), sodium (11.1% resp. 11.4%), C-reactive protein (CRP) (14.8% resp. 15.3%), blood pressure (5.0%), blood sugar (70.4% resp. 70.6%), body temperature (13.6% resp. 13.7%), SPI (45.6 resp. 45.3%), risk of falling (44.6% resp. 44.3%), risk of pneumonia (44.6% resp. 44.3%), Braden score (44.5% resp. 44.9%), body mass index (BMI) (35.1% resp. 34.1%), nutrition deficiency score (57.6% resp. 57.0%) and polymedication (9.6% resp. 9.5%). Table 1 and Tables S1a and S1b in the Supporting Information were created using the R package *{tableone}*.[32]

2.5 | Main outcome and measures

In the primary analysis, delirium was defined as an ICD-10 coded diagnosis (F05.0, F05.1, F05.8, F05.9) or a positive result on the Confusion Assessment Method (CAM). Since the ICD-10 code does not differentiate between delirium at admission and during hospitalisation, four researchers (A.L., V.B., S.S. and M.L.) developed a protocol in an iterative process on the data set from 2015 to 2016 and validated it on the set from 2017 to 2018. Then two assessors (R.K. and G.G.) independently reviewed charts of patients with an ICD-10 code for delirium using this protocol, blinded to information on drugs and the Delirium Observation Screening Scale (DOSS), and determined whether the patient had delirium on admission. A third reviewer (A.L.) resolved any disagreements. To measure agreement among the two assessors, we calculated unweighted Cohen's kappa, using *{kappa2}* on a third of the validation data set.[33] In the secondary analysis, we additionally considered a daily mean score of three points or more in the DOSS as a delirium during hospitalisation.

2.6 | Exposure

All drugs with a single active ingredient or combination products administered within the first 24 hours of hospitalisation were considered. The extracted raw data did not always contain machine-readable information on the active ingredients of the ordered drugs (i.e., non-standardised free-text entries). We mapped the medication orders to their active ingredient based on the Anatomical Therapeutic Chemical Classification System (World Health Organization, Geneva, Switzerland) following a semi-automated process as described by Siebenhüner et al.[34]

For each of the 19 ABSs identified and described in our systematic review,[8] the cumulative ACH burden score was calculated using a list of all drugs scored from our previously published study.[29] Drugs not scored in one of the ABSs were assumed to have no ACH activity (zero points). Four ABSs did not use a 4-point grading system (0: no to 3: high).[16,17,22,27] For the scale by Minzenberg et al.,[22] we set cut-offs at 10 points for the Pharmacological Index (PI) and 47 points for the Clinical Index (CI) by comparing the substances with the other ABSs. The high potency drugs in the scale of Duran et al. (DS) received a score of three, the low potency drugs a score of two, drugs listed in table 4[16] in that publication received a score of one, drugs in Annex Sublist 1[16] in that publication received a score of half a point. Last, we transformed the Anticholinergic Activity Scale (AAS)[17] as follows: four into three, three into two, two and one both into one, and zero remained zero. We did not convert the Anticholinergic Toxicity Scale (ATS)[27] because the scoring ranged between half a point and five points, which is similar to the points given by the other ABSs. Patients were classified into exposure groups based on each ABS: for the binary approach: no/low risk <3 or high risk ≥3, and for the categorical approach: no risk = 0, low risk 0.5 to <3, or high risk ≥3.

2.7 | Statistical analysis

All analyses were conducted using R version 3.6.2 and the integrated development environment R Studio.[35,36] The R functions and corresponding packages are denoted as function *{package}*.[36] Continuous variables included in the regression analysis containing missing variables were stratified as categorical using the hospital's laboratory standard values as described in Elsener et al.[37]

We calculated the variance inflation factor for each variable with vif *{car}*[38] to test for multicollinearity between the variables. The

TABLE 1 Example of patient characteristics using the ARS to stratify the exposure for the primary analysis. Details for the other ABS can be found in the Supporting Information

Characteristics	Primary analysis overall (*n*: 26 302)	ARS low <3 (*n*: 25 236)	ARS high ≥3 (*n*: 1066)
Total delirium cases, *n* (%)	864 (3.3)	785 (3.1)	79 (7.4)
Delirium DOSS	–	–	–
Delirium ICD-10 codes and CAM, *n* (%)	864 (3.3)	785 (3.1)	79 (7.4)
Age, mean years (± SD)	77.9 (7.6)	77.90 (7.66)	79.13 (7.56)
Age, *n* (%)			
65–75 years	10 792 (41.0)	10 437 (41.4)	355 (33.3)
76–85 years	10 654 (40.5)	10 173 (40.3)	481 (45.1)
86–95 years	4683 (17.8)	4461 (17.7)	222 (20.8)
>95 years	173 (0.7)	165 (0.7)	8 (0.8)
Female sex, *n* (%)	13 647 (51.9)	13 032 (51.6)	615 (57.7)
Department, *n* (%)			
Medical department	14 385 (54.7)	13 704 (54.3)	681 (63.9)
Surgical department	11 917	11 532 (45.7)	385 (36.1)
Length of stay, median days [IQR]	6.0 [4.0, 10.0]	6.00 [4.00, 10.00]	7.00 [4.00, 11.00]
Placement after discharge, *n* (%)			
Died	841 (3.2)	759 (3.0)	82 (7.7)
Home	6402 (24.3)	6235 (24.7)	167 (15.7)
Ambulatory follow-up treatment	10 725 (40.8)	10 425 (41.3)	300 (28.1)
Ambulatory homecare	2039 (7.8)	1928 (7.6)	111 (10.4)
Nursing homes	3267 (12.4)	2970 (11.8)	297 (27.9)
Rehabilitation centres	2923 (11.1)	2818 (11.2)	105 (9.8)
Unknown	105 (0.4)	101 (0.4)	4 (0.4)
Hearing device, *n* (%)			
None	15 286 (58.1)	14 646 (58.0)	640 (60.0)
Hearing device	4898 (11.0)	2780 (11.0)	118 (11.1)
Missing	*8118 (30.9)*	*7810 (30.9)*	*308 (28.9)*
Visual aid, *n* (%)			
None	4757 (18.1)	4514 (17.9)	243 (22.8)
Glasses or contacts	13 361 (50.8)	12 844 (50.9)	517 (48.5)
Missing	*8184 (31.1)*	*7878 (31.2)*	*306 (28.7)*
Acute myocardial infarction, *n* (%)	1396 (5.3)	1364 (5.4)	32 (3.0)
Congestive heart failure, *n* (%)	4486 (17.1)	4324 (17.1)	162 (15.2)
Peripheral vascular disease, *n* (%)	3578 (13.6)	3441 (13.6)	137 (12.9)
Cerebrovascular disease, *n* (%)	3279 (12.5)	3145 (12.5)	134 (12.6)
Dementia, *n* (%)	2164 (8.5)	1911 (7.6)	253 (23.7)
COPD, *n* (%)	2948(11.2)	2839 (11.2)	109 (10.2)
Rheumatoid disease, *n* (%)	778 (3.0)	749 (3.0)	29 (2.7)
Peptic ulcer disease, *n* (%)	518 (2.0)	492 (1.9)	26 (2.4)
Liver disease, *n* (%)	505 (1.9)	489 (1.9)	16 (1.5)
Diabetes, *n* (%)	5511 (21.0)	5291 (21.0)	220 (20.6)
Hemiplegia, paraplegia, *n* (%)	1158 (4.4)	1087 (4.3)	71 (6.7)
Renal dysfunction, *n* (%)	5898 (22.4)	5632 (22.3)	266 (25.0)
Cancer, *n* (%)	4550 (17.3)	4340 (17.2)	210 (19.7)
SPI, median [IQR]	39.0 [35.0, 40.0]	39.00 [35.00, 40.00]	34.00 [26.00, 39.00]

TABLE 1 (Continued)

Characteristics	Primary analysis overall (*n*: 26 302)	ARS low <3 (*n*: 25 236)	ARS high ≥3 (*n*: 1066)
Risk of falling, *n* (%)			
No	5410 (20.6%)	5298 (21.0)	112 (10.5)
Yes	9156 (34.8%)	8633 (34.2)	523 (49.1)
Missing	*11 736 (44.6%)*	*11 305 (44.8)*	*431 (40.4)*
Risk of pneumonia, *n* (%)			
No	9831 (37.4%)	9519 (37.7)	312 (29.3)
Yes	4735 (18.0%	4412 (17.5)	323 (30.3)
Missing	*11 736 (44.6%)*	*11 305 (44.8)*	*431 (40.4)*
Braden score, median [IQR]	22.0 [20.0, 23.0]	22.00 [20.00, 23.00]	20.00 [17.00, 22.00]
Nutrition deficiency score, median [IQR]	1.0 [1.0, 2.0]	1.00 [1.00, 2.00]	1.00 [1.00, 3.00]
Catheterisation, *n* (%)	7495 (28.5)	7172 (28.4)	323 (30.3)
Surgery during stay, *n* (%)	8610 (32.7)	8390 (33.2)	220 (20.6)
GFR [ml/min], median [IQR]	64.0 [45.0, 80.0]	64.00 [45.00, 80.00]	63.00 [44.50, 81.00]
Creatinine [μmol/l], median [IQR]	87.0 [70.0, 115.2]	87.00 [70.00, 115.50]	85.00 [66.50, 113.00]
Sodium [mmol/l], median [IQR]	138.0 [135.0, 140.0]	138.00 [135.00, 140.00]	138.00 [135.00, 140.00]
Potassium [mmol/l], median [IQR]	4.1 [3.8, 4.4]	4.05 [3.80, 4.35]	4.05 [3.70, 4.35]
ALAT [U/l], median [IQR]	20.0 [14.0, 35.0]	20.00 [14.00, 36.00]	18.00 [12.00, 30.25]
ASAT [U/l], median [IQR]	25.0 [20.0, 35.0]	25.00 [20.00, 35.00]	25.00 [19.50, 33.00]
CRP [mg/l], median [IQR]	12.0 [2.6, 55.8]	12.00 [2.60, 55.00]	17.10 [4.00, 65.00]
CRP [mg/l], *n* (%)			
< 5	7795 (29.6)	7511 (29.8)	284 (26.6)
5–10	2651 (10.1)	2539 (10.1)	112 (10.5)
10–50	5955 (22.6)	5662 (22.4)	293 (27.5)
>50	6005 (22.8)	5709 (22.6)	296 (27.8)
Missing	*3896 (14.8)*	*3815 (15.1)*	*81 (7.6)*
Temperature [°C], median [IQR]	36.6 [36.2, 36.9]	36.55 [36.23, 36.90]	36.60 [36.30, 36.97]
Systolic blood pressure [mmHg], mean (±SD)	134.2 (19.7)	134.35 (19.71)	131.33 (19.88)
Diastolic blood pressure [mmHg], mean (±SD)	71.9 (11.6)	72.00 (11.63)	70.18 (11.40)
Blood sugar [mmol/l], median [IQR]	6.9 [5.85, 8.7]	6.92 [5.85, 8.73]	6.73 [5.80, 8.30]
BMI, mean (±SD)	26.1 (5.3)	26.15 (5.24)	25.20 (5.50)
Polymedication, mean (±SD)	7.6 (3.8)	7.40 (3.77)	10.67 (3.79)
ACH burden per scale, mean (±SD)	0.34 (0.99)	0.18 (0.48)	4.19 (1.81)

SD: standard deviation, IQR: interquartile range, DOSS: Delirium Observation Screening Score, CAM: Confusion Assessment Method, COPD: chronic obstructive pulmonary disease, SPI: self-care index, GFR: glomerular filtration rate, ALAT: alanine transaminase, ASAT: aspartate transaminase, CRP: C-reactive protein, BMI: body mass index, ACH: anticholinergic.

generalised variance inflation factor (GVIF) was calculated instead in case variables had more than two degrees of freedom (df). Variables were excluded from the multivariable regression analyses if $GVIF^{\left(\frac{1}{2\times df}\right)}>10$.

A logistic regression model was used with a logit-link function for the outcome delirium. We performed univariable and multivariable analyses adjusting for co-variables that were selected based on prior work.[8] Since we allowed multiple hospitalisations for participants, we conducted a sensitivity analysis considering only the first hospitalisation of each participant (Supplementary 4 in the Supporting Information). Furthermore, we performed a time-to-event analysis using Cox regression (Supplementary 5 in the Supporting Information) to evaluate whether there is a difference at which rate patients develop delirium over time.

3 | RESULTS

Out of 130 105 patients aged 65 years or older hospitalised for longer than 48 hours, 26 302 were included in the primary and 25 279 in the secondary analysis. The mean age was 77.9 ± 7.6 years and 51.9% were women. In the primary analysis, 864 (3.3%) developed

delirium during hospitalisation and 1201 (4.6%, Anticholinergic Toxicity Scale [ATS]) to 16 504 (62.7%, German Anticholinergic Burden Scale [GABS]) patients were exposed to drugs with ACH properties. Considering the DOSS in the secondary analysis led to 1906 additional cases, representing a total of 2770 (11.0%) delirious patients with 1041 (4.1%, Anticholinergic Toxicity Scale [ATS]) to 15 752 (62.3%, German Anticholinergic Burden Scale [GABS]) (Figure 1) patients being exposed. Delirium occurred with a median of 3.5 days (IQR 1–4 days) after admission. The top five drugs used in the entire cohort that were evaluated by the vast majority of ABSs were quetiapine, haloperidol, fentanyl, loperamide and tizanidine. When looking at participants with and without delirium separately, delirious patients used more olanzapine, amitriptyline, amantadine and solifenacin. These observations were true using both delirium definitions. Patient characteristics stratified by exposure using the Anticholinergic Risk Scale (ARS) as an example are summarised in Table 1. For the other 18 ABSs the patient characteristics are depicted in Tables S1a, S1b, S2a and S2b in the Supporting Information. Additionally, a graph of the study design can be found in Figure S3 in the Supporting Information. We did not detect any collinearity between the variables. Cohen's kappa for delirium diagnosis at admission was calculated for one third of the validation cohort and resulted in 0.77, which is considered as 'substantial' agreement between assessors.[39]

3.1 | Primary analysis with outcome delirium defined by ICD-10 and CAM

In the primary analysis adjusted for the co-variables age, sex, dementia, catheterisation and categorical CRP, 14 out of the 19 ABSs indicated that a high cumulative ACH burden is significantly associated with the development of delirium during hospitalisation compared to patients with low burden (Table 2, Tables S3.1 and S3.2). The largest effect size was observed with the ATS. Similar results were observed in the categorical analysis regarding the comparison of no risk versus high risk. Additionally, we could see three ABSs (Cancelli's Anticholinergic Burden Scale [CABS], Anticholinergic Activity Scale [AAS], ARS) showing a significant association with delirium when comparing low to no ACH burden, which was not observed using the other ABSs (Table 3).

The sensitivity analysis for the binary approach considering only the first hospitalisation of each participant revealed in 13 ABSs an association; however, only six ABSs (ACB, ARS, ACL, CrAS, PI and CI) showed a significant result while one ABS (SCDL) had a reverse effect.

3.2 | Secondary analysis with delirium defined by ICD-10, CAM and DOSS

By improving the definition of delirium diagnosis through the consideration of the DOSS, the secondary analysis adjusted to the same co-variables showed 16 out of 19 ABSs to be significantly associated with the development of delirium during hospitalisation when comparing high to low ACH burden (Table 2, Tables S3.1 and S3.2 in the Supporting Information). The two additional ABSs, which became significant compared to the primary analysis, were the Anticholinergic Effect on Cognition (AEC) and Anticholinergic Drug Scale (ADS). The results in the categorical approach represent the same findings as in the primary analysis with more ABSs also being significantly

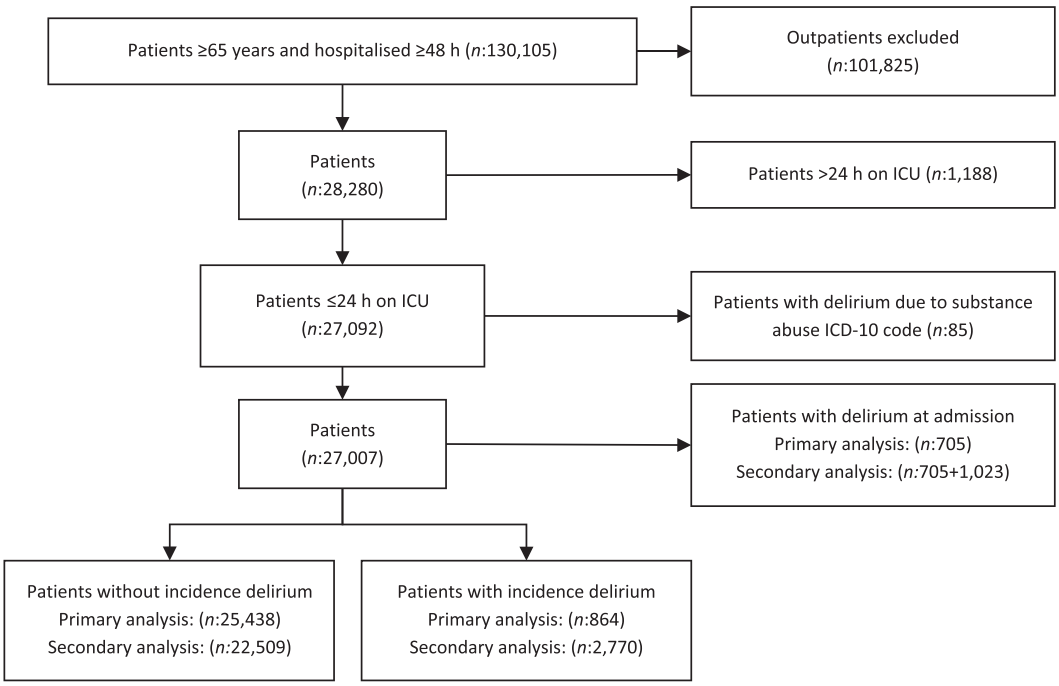

FIGURE 1 Flowchart of included and excluded patients for primary and secondary analysis

TABLE 2 Multivariable regression using the binary approach for the outcome delirium in the primary and secondary analysis

Scale	Primary analysis multivariable		Low <3 *n* (delirium [%])	High ≥3	Secondary analysis multivariable		Low <3 *n* (delirium [%])	High ≥3
	OR	95% CI			OR	95% CI		
ABC[10]	1.13	0.88, 1.44	24 622 (784 [3.2])	1680 (80 [4.8])	0.99	0.84, 1.15	23 670 (2534 [10.7])	1609 (236 [14.7])
AEC[11]	1.28	1.00, 1.61	24 950 (772 [3.1])	1352 (92 [6.8])	**1.92**	**1.63, 2.25**	24 131 (2481 [10.3])	1148 (289 [25.2])
ACB[13]	**1.46**	**1.25, 1.70**	21 610 (596 (2.8))	4692 (268 [5.7])	**1.62**	**1.46, 1.79**	20 993 (1985 [9.5])	4286 (785 [18.3])
AIS[12]	**1.26**	**1.09, 1.46**	18 943 (531 (2.8))	7359 (333 [4.5])	**1.50**	**1.37, 1.64**	18 400 (1706 [9.3])	6879 (1064 [15.5])
CABS[14]	0.84	0.66, 1.07	24 102 (783 [3.2])	2200 (81 [3.7])	*0.86*	*0.74, 0.99*	23 173 (2496 [10.8])	2106 (274 [13.0])
Chew[16]	**1.53**	**1.26, 1.85**	23 954 (720 [3.0])	2348 (144 [6.1])	**1.71**	**1.50, 1.94**	23 115 (2337 [10.1])	2164 (443 [20.0])
AAS[18]	1.05	0.85, 1.28	23 764 (745 [3.1])	2538 (119 [4.7])	1.03	0.90, 1.18	22 891 (2407 [10.5])	2388 (363 [15.2])
ARS[25]	**1.52**	**1.17, 1.95**	25 236 (785 [3.1])	1066 (79 [7.4])	**2.43**	**2.03, 2.90**	24 365 (2527 [10.4])	914 (243 [26.6])
ACL[26]	**1.60**	**1.28, 1.97**	24 309 (753 [3.1])	1993 (111 [5.6])	**1.92**	**1.66, 2.20**	23 426 (2430 [10.4])	1853 (340 [18.3])
CrAS[19]	**1.66**	**1.40, 1.97**	22 849 (653 [2.9])	3453 (211 [6.1])	**2.03**	**1.81, 2.27**	22 159 (2152 [9.7])	3120 (618 [19.8])
ADS[15]	1.19	0.97, 1.46	23 234 (745 [3.2])	3068 (119 [3.9])	**1.32**	**1.16, 1.49**	22 343 (2368 [10.6])	2936 (402 [13.7])
SCDL[27]	0.82	0.64, 1.03	23 057 (782 [3.4])	3245 (82 [2.5])	1.09	0.95, 1.24	22 169 (2445 [11.0])	3110 (325 [10.5])
PI[23]	**1.67**	**1.37, 2.02**	24 498 (698 [2.8])	1804 (166 [9.2])	**2.51**	**2.19, 2.88**	23 793 (2296 [9.6])	1486 (474 [31.9])
CI[23]	**1.73**	**1.42, 2.09**	24 625 (701 [2.8])	1677 (163 [9.7])	**2.63**	**2.28, 3.03**	23 917 (2314 [9.7])	1362 (456 [33.5])
GABS[22]	**1.33**	**1.15, 1.53**	18 212 (496 [2.7])	8090 (368 [4.5])	**1.50**	**1.37, 1.64**	17 707 (1621 [9.2])	7572 (1149 [15.2])
DS[17]	**1.22**	**1.05, 1.41**	18 901 (540 [2.9])	7401 (324 [4.4])	**1.53**	**1.39, 1.67**	18 340 (1701 [9.3])	6939 (1069 [15.4])
BAADS[24]	**1.24**	**1.07, 1.44**	18 552 (522 [2.8])	7750 (342 [4.4])	**1.44**	**1.31, 1.57**	18 021 (1684 [9.3])	7258 (1086 [15.0])
KABS[21]	**1.31**	**1.12, 1.53**	20 989 (606 [2.9])	5313 (258 [4.9])	**1.55**	**1.40, 1.71**	20 371 (1963 [9.6])	4908 (807 [16.4])
ATS[28]	**1.91**	**1.48, 2.45**	25 506 (776 [3.0])	796 (88 [11.1])	**3.05**	**2.50, 3.70**	24 623 (2530 [10.3])	656 (240 [36.6])
DRS[20]	**1.21**	**1.03, 1.42**	20 956 (614 [2.9])	5346 (250 [4.7])	**1.64**	**1.48, 1.80**	20 338 (1923 [9.5])	4941 (847 [17.1])

Notes: Far-left column: individual ABS; two columns on right to each analysis: absolute number of patients and percentage of prevalence of delirium developed during hospitalisation for each group. Multivariable analysis is adjusted for age, sex, dementia, categorical CRP and catheter use. ABC: Anticholinergic Burden Classification, AEC: Anticholinergic Effect on Cognition,[c]ACB: Anticholinergic Cognitive Burden Scale, AIS: Anticholinergic Impregnation Scale, CABS: Cancelli's Anticholinergic Burden Scale, AAS: Anticholinergic Activity Scale, ARS: Anticholinergic Risk Scale, ACL: Anticholinergic Loading Scale, CrAS: Clinician-rated Anticholinergic Scale, ADS: Anticholinergic Drug Scale, SCDL: Summer's Class of Drug List, PI and CI: Minzenberg's Pharmacological index (PI) and Clinical Index (CI), GABS: German Anticholinergic Burden Scale, DS: Durán Scale, BAADS: Brazilian Anticholinergic Activity Drug Scale, KABS: Korean Anticholinergic Burden Scale, ATS: Anticholinergic Toxicity Scale, DRS: Delirogenic Risk Scale.

associated when comparing no to low ACH burden in the secondary analysis (Table 3).

The sensitivity analysis for the binary approach considering only the first hospitalisation revealed the same results as the analysis including multiple hospitalisations.

4 | DISCUSSION

We found that a high cumulative ACH burden score of three or more points measured with 14, respectively 16, out of 19 ABSs was significantly associated with incident delirium in older hospitalised patients.

Delirium is a multifactorial syndrome and a preventable source of morbidity and mortality. With respect to the neurotransmitter hypothesis, drugs with ACH properties may induce an ACH deficiency leading to delirium. Therefore, various ABSs have been developed to quantify the cumulative ACH burden in a patient by scoring each substance from zero (no) to three (high ACH properties) points and thus to guide clinicians in their evaluation of ADEs, such as delirium.

Possible reasons for the disparity in the results between scales are twofold. First, this could be due to the differences within the ABSs, their quality, the amount of drugs scored and the cut-offs used. Second, it could be due to the difficulty of diagnosing delirium.

The ABSs have been developed at different time points, score an unequal number of drugs and follow diverse scoring rules. Amitriptyline is the only drug that was scored unanimously with a score of three in all ABSs. The oldest scale—Summer's Class of Drug List (SCDL)—was developed in 1978, and the newest—Brazilian Anticholinergic Activity Scale (BAADS)—was published in 2019. Starting in 2011, seven newer ABSs—Duran Scale (DS), Delirogenic Risk Scale (DRS), Anticholinergic Impregnation Scale (AIS), GABS, Korean Anticholinergic Burden Scale (KABS), Anticholinergic Loading Scale (ACL), BAADS—appeared that were all built on previously published scales, in contrast to the older ABSs from the early 2000s, which were primarily single studies using different methods for scale development ranging from expert opinions to SAA. All the review-based scales showed a significant association when comparing high to low ACH burden. However, the associations observed were not necessarily

TABLE 3 Multivariable regression using the categorical approach for the outcome delirium

	Primary analysis multivariable			Secondary analysis multivariable		
Scale	**OR**	**95% CI**	**Exposed *n* (delirium [%])**	**OR**	**95% CI**	**Exposed *n* (delirium [%])**
ABC[10]						
No burden	*Reference*		24 374 (778 [3.2])	*Reference*		23 428 (2512 [10.7])
Low burden	0.77	0.30, 1.61	248 (6 [2.4])	0.83	0.51, 1.31	242 (22 [9.1])
High burden	1.13	0.88, 1.44	1680 (80 [4.8])	0.98	0.84, 1.15	1609 (236 [14.7])
AEC[11]						
No burden	*Reference*		20 327 (577 [2.8])	*Reference*		19 750 (1867 [9.5])
Low burden	1.14	0.96, 1.35	4623 (195 [4.2])	**1.22**	**1.10, 1.36**	4381 (614 [14.0])
High burden	**1.32**	**1.03, 1.68**	1352 (92 [6.8])	**2.01**	**1.70, 2.36**	1148 (289 [25.2])
ACB[13]						
No burden	*Reference*		15 680 (436 [2.8])	*Reference*		15 240 (1384 [9.1])
Low burden	0.90	0.74, 1.08	5930 (160 [2.7])	1.11	1.00, 1.24	5753 (601 [10.4])
High burden	**1.42**	**1.20, 1.67**	4692 (268 [5.7])	**1.67**	**1.50, 1.86**	4286 (785 [18.3])
AIS[12]						
No burden	*Reference*		11 262 (333 [3.0])	*Reference*		10 958 (1005 [9.2])
Low burden	0.86	0.72, 1.04	7681 (198 [2.6])	1.06	0.95, 1.18	7442 (701 [9.4])
High burden	**1.19**	**1.01, 1.40**	7359 (333 [4.5])	**1.53**	**1.38, 1.70**	6879 (1064 [15.5])
CABS[14]						
No burden	*Reference*		22 765 (716 [3.1])	*Reference*		21 891 (2292 [10.5])
Low burden	**1.33**	**1.01, 1.72**	1337 (67 [5.0])	**1.31**	**1.10, 1.55**	1282 (204 [15.9])
High burden	0.86	0.67, 1.09	2200 (81 [3.7])	0.88	0.76, 1.02	2106 (274 [13.0])
Chew[16]						
No burden	*Reference*		18 192 (490 [2.7])	*Reference*		17 722 (1563 [8.8])
Low burden	1.07	0.91, 1.27	5762 (230 [4.0])	**1.33**	**1.20, 1.47**	5393 (774 [14.4])
High burden	**1.56**	**1.28, 1.91**	2348 (144 [6.1])	**1.86**	**1.63, 2.12**	2164 (433 [20.0])
AAS[18]						
No burden	*Reference*		21 371 (585 [2.7])	*Reference*		20 773 (1924 [9.3])
Low burden	**1.44**	**1.19, 1.74**	2393 (160 [6.7])	**1.86**	**1.64, 2.12**	2118 (483 [22.8])
High burden	1.12	0.91, 1.38	2538 (119 [4.7])	1.14	0.99,1.30	2388 (363 [15.2])
ARS[25]						
No burden	*Reference*		21 644 (573 [2.6])	*Reference*		21 082 (1861 [8.8])
Low burden	**1.53**	**1.28, 1.81**	3592 (212 [5.9])	**1.93**	**1.73, 2.15**	3283 (666 [20.3])
High burden	**1.71**	**1.31, 2.20**	1066 (79 [7.4])	**2.77**	**2.32, 3.30**	914 (243 [26.6])
ACL[26]						
No burden	*Reference*		18 961 (550 [2.9])	*Reference*		18 348 (1743 [9.5])
Low burden	1.17	0.99, 1.39	5348 (203 [3.8])	**1.36**	**1.22, 1.51**	5078 (687 [13.5])
High burden	**1.67**	**1.33, 2.07**	1993 (111 [5.6])	**2.08**	**1.80, 2.40**	1853 (340 [18.3])
CrAS[19]						
No burden	*Reference*		16 291 (454 [2.8])	*Reference*		15 837 (1444 [9.1])
Low burden	1.02	0.85, 1.21	6558 (199 [3.0])	**1.22**	**1.10, 1.335**	6322 (708 [11.2])
High burden	**1.67**	**1.40, 1.99**	3453 (211 [6.1])	**2.08**	**1.80, 2.40**	3120 (618 [19.8])
ADS[15]						
No burden	*Reference*		15 803 (532 [3.4])	*Reference*		15 202 (1629 [10.7])
Low burden	0.91	0.77, 1.07	7431 (213 [2.9])	1.06	0.96, 1.18	7141 (739 [10.3])
High burden	1.16	0.93, 1.42	3068 (119 [3.9])	**1.34**	**1.18, 1.53**	2936 (402 [13.7])

TABLE 3 (Continued)

Scale	Primary analysis multivariable			Secondary analysis multivariable		
	OR	95% CI	Exposed *n* (delirium [%])	OR	95% CI	Exposed *n* (delirium [%])
SCDL[27]						
No burden	*Reference*		16 944 (590 [5.3])	*Reference*		16 276 (1806 [11.1])
Low burden	*0.82*	*0.69, 0.97*	6113 (192 [3.1])	0.86	0.78, 0.96	5893 (639 [10.8])
High burden	*0.77*	*0.60, 0.98*	3245 (82 [2.5])	1.05	0.91, 1.20	3110 (325 [10.5])
PI[23]						
No burden	*Reference*		24 436 (698 [2.9])	*Reference*		23 738 (2285 [9.6])
Low burden	-	-	62 (0 [0])	**2.49**	**1.13, 5.05**	55 (11 [20.0])
High burden	**1.66**	**1.37, 2.01**	1804 (166 [9.2])	**2.52**	**2.19, 2.89**	1486 (474 [31.9])
CI[23]						
No burden	*Reference*		24 467 (696 [2.8])	*Reference*		23 773 (2272 [9.6])
Low burden	0.61	0.21, 1.37	158 (5 [3.2])	**2.52**	**1.63, 3.81**	144 (42 [29.2])
High burden	**1.71**	**1.40, 2.08**	1677 (163 [9.7])	**2.66**	**2.31, 3.06**	1362 (456 [33.5])
GABS[22]						
No burden	*Reference*		9798 (295 [3.0])	*Reference*		9527 (876 [9.2])
Low burden	*0.80*	*0.66, 0.96*	8414 (201 [2.4])	1.03	0.92, 1.15	8180 (745 [9.1])
High burden	**1.22**	**1.03, 1.44**	8090 (368 [4.5])	**1.52**	**1.37, 1.69**	7572 (1149 [15.2])
DS[17]						
No burden	*Reference*		11 131 (312 [2.8])	*Reference*		10 843 (972 [9.0])
Low burden	*1.00*	*0.84, 1.19*	7770 (228 [2.9])	1.07	0.96, 1.20	7497 (729 [9.7])
High burden	**1.22**	**1.03, 1.44**	7401 (324 [4.4])	**1.57**	**1.42, 1.74**	6939 (1069 [15.4])
BAADS[24]						
No burden	*Reference*		10 988 (316 [22.9])	*Reference*		10 698 (945 [8.8])
Low burden	0.91	0.76, 1.10	7564 (206 [2.7])	**1.17**	**1.04, 1.30**	7323 (739 [10.1])
High burden	**1.20**	**1.02, 1.41**	7750 (342 [4.4])	**1.53**	**1.38, 1.70**	7258 (1086 [15.0])
KABS[21]						
No burden	*Reference*		14 004 (388 [2.8])	*Reference*		13 635 (1197 [8.8])
Low burden	1.05	0.88, 1.24	6985 (218 [3.1])	**1.29**	**1.16, 1.43**	6736 (766 [11.4])
High burden	**1.34**	**1.13, 1.58**	5313 (258 [4.9])	**1.69**	**1.52, 1.88**	4908 (807 [16.4])
ATS[28]						
No burden	*Reference*		25 101 (765 [3.0])	*Reference*		24 238 (2475 [10.2])
Low burden	0.84	0.43, 1.48	405 (11 [2.7])	**1.47**	**1.06, 2.00**	385 (55 [14.3])
High burden	**1.90**	**1.47, 2.44**	796 (88 [11.1])	**3.07**	**2.52, 3.73**	656 (240 [36.6])
DRS[20]						
No burden	*Reference*		13 227 (384 [2.9])	*Reference*		12 876 (1148 [8.9])
Low burden	0.94	0.79, 1.11	7729 (230 [3.0])	1.11	1.00, 1.23	7462 (775 [10.4])
High burden	1.18	0.99, 1.40	5346 (250 [4.7])	**1.70**	**1.53, 1.89**	4941 (847 [17.1])

Notes: Far-left column: individual ABS; two columns on right to each analysis: absolute number of patients and percentage of prevalence of delirium developed during hospitalisation for each group. Multivariable analysis is adjusted for age, sex, dementia, categorical CRP and catheterisation. ABC: Anticholinergic Burden Classification, AEC: Anticholinergic Effect on Cognition, ACB: Anticholinergic Cognitive Burden Scale, AIS: Anticholinergic Impregnation Scale, CABS: Cancelli's Anticholinergic Burden Scale, AAS: Anticholinergic Activity Scale, ARS: Anticholinergic Risk Scale, ACL: Anticholinergic Loading Scale, CrAS: Clinician-rated Anticholinergic Scale, ADS: Anticholinergic Drug Scale, SCDL: Summer's Class of Drug List, PI and CI: Minzenberg's Pharmacological index (PI) and Clinical Index (CI), GABS: German Anticholinergic Burden Scale, DS: Durán Scale, BAADS: Brazilian Anticholinergic Activity Drug Scale, KABS: Korean Anticholinergic Burden Scale, ATS: Anticholinergic Toxicity Scale, DRS: Delirogenic Risk Scale.

stronger with the review-based scales but comparable to each other and consistent in both approaches. The reason for this is probably the fact that older scales scored fewer drugs and more drugs with high numbers of points, while newer, review-based scales evaluated more drugs and of these scored more with only half to one point. Thus, it is important to calculate the cumulative ACH burden in a patient, since

three drugs with a score of one point are considered as high burden. It is therefore essential to investigate additional drugs for their ACH property when developing a new scale. In our previous review, we assessed the quality of the ABSs using a systematic approach.[8] Regarding the scales with the best quality (Anticholinergic Cognitive Burden Scale [ACB], DS, GABS and AEC), three showed a significant association.

A surprising and outstanding result was observed for the ATS, which used a computational scoring approach where the Morgan algorithm calculates the Tanimoto coefficient, that represents drug–receptor inhibition propensity and accounts for pharmacodynamics interactions.[27] So far, no validation exists that uses the ATS, which might raise the question whether a completely objective ABS that is based purely on computational receptor affinities is better than others that consider side effects or expert opinions when planning to score new substances.

Previous cohort studies investigated the association of seven ABSs with delirium.[40–52] While the ARS and DS showed an association with delirium in all previous studies,[41,43,44,47,48] the ACB and ADS demonstrated contradicting results.[40,42,44,50–52] The Chew, CrAS and SCDL have so far not been associated with delirium.[44–46] However, not all of these studies can be compared to ours. Wolters et al.,[48] Burry et al.,[41] Rigor et al.[51] and Vondeling et al.,[52] investigating the ADS, ARS, DS and ACB, studied delirium in ICU patients, which were excluded from this report. Egberts et al.,[44] evaluating the ACB, ARS and Chew, focused on delirium at hospital admission, which was also excluded from our study. Han and McCusker[45] used the CrAS and SCDL to study the change in severity of symptoms in patients with pre-existing delirium and Landi et al.[47] studied patients in nursing homes, both circumstances that were not considered in our analysis. Another five previous studies evaluating three ABSs (ACB, ARS and CrAS) in clinical settings focused on specific populations, such as palliative patients,[49] patients with Parkinson's disease,[43] patients with hip fracture,[46] and patients with cognitive impairment[42] or under treatment for dementia.[40] The final study comparable to ours is the one by Rawle et al.,[50] which studied patients aged 70 and older that were admitted to the hospital through the emergency department and that were hospitalised for a minimum of 48 hours. In contrast to our results, they did not find an association between the ACB and delirium.

Our study confirmed the association with delirium previously observed in the studies by Ah et al.[40] using the ACB, and by Crispo et al.[43] and Zimmerman et al.[49] using the ARS. Additionally, we were able to demonstrate a significant association with delirium using the CrAS compared to earlier findings by Juliebo et al.[46] For all the other ABSs, this study is the first to our knowledge to study non-ICU older patients in an acute care hospital comprehensively using published ABSs to evaluate their association with delirium developed during hospitalisation.

Results of the categorical analysis exhibit no significant association with increased delirium risk when comparing low to no ACH burden, with some exceptions. This opens the question whether a cut-off of three points or more is valid. In most studies, this is applied because the scales themselves define a single substance with a score of three points as high ACH burden. However, this cut-off may differ depending on which ABS is used and what outcome is studied.

4.1 | Delirium diagnosis definition

Current evidence suggests that delirium is heavily underdiagnosed and underreported, which could induce misclassification bias.[53,54] The reasons for this could be its fluctuating course, the extensive range of symptoms, the lack of knowledge and training of nurses and physicians to recognise it or how to use the screening or detection tools correctly.[54–56] The fact that delirium is a purely clinical diagnosis, without laboratory tests at hand, has resulted in numerous such tools, which have been developed for different purposes (screening, detection or severity assessment) and different clinical settings (ICU, emergency room, medical ward). A recent systematic review by Helfand et al. identified 49 tools of which 30 are for non-ICU patients.[57] Of these, the authors recommend the CAM, DOSS, Delirium Rating Scale Revised 98 and Memorial Delirium Assessment Scale for delirium identification. Using the DOSS might indicate delirium; however, according to the authors, it should be confirmed by a physician. At our hospital nurses assess the DOSS three times a day and, if the daily mean is equal to or larger than three points, a physician should confirm the diagnosis by performing the CAM. Even though the DOSS is considered only a screening tool,[57] its sensitivity and specificity of 90% and 92%, respectively, is high.[58] This is comparable to the CAM (diagnostic tool), which has a sensitivity of 82% and a specificity of 99%.[59] Considering only ICD-10 diagnosis codes and the CAM, our delirium rate would have dropped to 3.3%, which is below the reported range of 6% to 56%.[1] In regard to the problem of underdiagnosing of delirium and the high performance measures of the DOSS, inclusion of the DOSS in the delirium definition might have minimised misclassification and strengthened the findings. Nevertheless, a prospective study using a diagnostic tool would still be warranted to confirm our results.

4.2 | Strengths

The study population sample size is substantially larger than in previous studies and we controlled for measured confounding by adjusting for covariables. In addition to the medication list by entry, the free-text entries for single substances and combinations were comprehensively mapped to their ingredients, thereby maximising the consideration of all drug orders. Another positive aspect of this study is the reporting of the two analyses on both definitions of the outcome delirium and the fact that the results are similar, which strengthens the results found. Results also did not differ much when conducting the sensitivity analysis or the Cox regression, evaluating whether the rate of people developing delirium over time is different in exposed and unexposed participants.

4.3 | Limitations

This was a retrospective single-centre study. We did not consider the dosage or route of administration; however, so far, the application of ABSs has been independent of the dosage or the route of administration. Additionally, we neither considered medication taken prior to admission nor over-the-counter drugs, which would not have been possible to identify with our data set. This might have contributed to limited selection bias. However, if chronic medications are taken prior to admission, these would generally be carried on during hospitalisation and thus would be registered at admission. The exposure also strongly depended on the nurses' documentation. If administration of medication was not noted, it was not represented in our data set. However, we believe documentation is recorded quite rigorously due to the use of bedside terminal computers allowing for direct bedside documentation and little distortion between the time sequence of events, therefore reflecting reality better than if we had only considered prescribed data.[60,61] Still, clinical conclusions must be drawn carefully because EHR studies only capture routinely documented outcomes. The nature of data collection in EHR studies may therefore contribute to outcome misclassification. The true number of patients with delirium may have been higher in our setting for two reasons: (i) delirium is a fluctuating outcome[1] known to be underreported,[54] and (ii) we excluded high-risk patients staying >24 hours in ICUs. Therefore, it is possible that our models underestimated the true effect size of ACH drugs triggering a delirium. However, we minimised the risk for missing delirium cases by considering three data sources for the outcome delirium, which is a strength of this work. Nevertheless, applying the exclusion criteria (ii) could have led to potential selection bias, and censoring upon ICU transfer would have been a solution to address this problem. Unfortunately, our dataset did not contain the date of ICU transfer, only the number of hours spent was available. Further, drug data upon admission might only be associated with delirium development within a short period of time, because ACH burden and other risk factors might change over the course of the hospital stay. In our cohort, delirium occurred within a median of 3.5 days after admission (IQR 1–4 days), which appears to be a reasonable timeframe to assess possible associations. Lastly, a specific ABS for Switzerland has not yet been developed, potentially leading to incomplete or incorrect scoring due to the different drugs available nationally.

5 | CONCLUSION

A cumulative ACH burden score of three points or more can be considered a high burden, which was statistically significantly and independently associated with the development of delirium during hospitalisation. The ABSs are convenient clinical tools to measure the ACH burden in hospitalised patients. Newer high-quality ABSs built from previously published scales seem to perform better. However, cut-off values might differ depending on the scale and outcome studied. Discontinuing or substituting drugs with an ACH score of three points or more upon admission might be a targeted intervention to reduce the risk of delirium development. However, it should be noted that delirium is a multifactorial syndrome, and that drugs are only one factor to be considered in delirium prevention. Further studies should be conducted in order to prospectively verify whether discontinuing drugs with ACH properties might reduce delirium occurrences.

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COMPETING INTERESTS

The authors declare they have no conflicts of interest.

CONTRIBUTORS

A.L., C.C. and M.L. conceived, designed the study and analysed the results. A.L., G.G. and R.K. preformed data management and P.E.B. performed mapping of free-text entries. A.L., V.B., R.K., G.G., S.S. and M.L. developed and applied the protocol for delirium diagnosis identification. A.L. drafted the manuscript and V.B., G.G., R.K., S.S., P.E.B., C.C. and M.L. revised the manuscript. All authors approved the final version to be submitted.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or the Supporting Information.

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