

High anticholinergic burden at admission associated with in-hospital mortality in older patients: A comparison of 19 different anticholinergic burden scales

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Abstract

Although no gold standard exists to assess a patient's anticholinergic burden, a review identified 19 anticholinergic burden scales (ABSs). No study has yet evaluated whether a high anticholinergic burden measured with all 19 ABSs is associated with in-hospital mortality and length of stay (LOS). We conducted a cohort study at a Swiss tertiary teaching hospital using patients' electronic health record data from 2015–2018. Included were patients aged ≥ 65 years, hospitalised ≥ 48 h without stays and >24 h in intensive care. Patients' cumulative anticholinergic burden score was classified using a binary (<3 : low, ≥ 3 : high) and categorical approach (0: no, 0.5–3: low, ≥ 3 : high). In-hospital mortality and LOS were analysed using multivariable logistic and linear regression, respectively. We included 27,092 patients (mean age 78.0 ± 7.5 years, median LOS 6 days). Of them, 913 died. Depending on the evaluated ABS, 1370 to 17,035 patients were exposed to anticholinergics. Patients with a high burden measured by all 19 ABSs were associated with a 1.32- to 3.03-fold increase in in-hospital mortality compared with those with no/low burden. We obtained similar results for LOS. To conclude, discontinuing drugs with anticholinergic properties (score ≥ 3) at admission might be a targeted intervention to decrease in-hospital mortality and LOS.

KEYWORDS

anticholinergic burden, in-hospital mortality, length of stay, older patients

1 | INTRODUCTION

With an ageing population, medical practice has changed over the past decades, as a drastic increase in polypharmacy has accompanied multimorbidity. The number of people taking at least five drugs has increased from

12% to 49% within the recent 20 years.¹ Hence, it is not surprising that the prevalence of drug use with potent anticholinergic (ACH) activity has nearly doubled in the last two decades.² Drugs with ACH properties block acetylcholine by binding to its receptor in the peripheral and central nervous system. Though some medications are

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used intentionally for their ACH action, others have ACH activity unrelated to their mechanisms of action. Older patients are in particular susceptible to ACH-related adverse drug events (ADEs) due to physiological changes in pharmacokinetics and pharmacodynamics as well as ACH hypersensitivity.³

At present, no gold standard exists to assess the ACH burden of a patient. Rudd et al. stated that expert-based lists are the sole clinically useful tool to quantify the ACH burden.⁴ These lists, called anticholinergic burden scales (ABSs), generally assign a number from one (low) to three (high) points to each substance. The cumulative ACH burden for a patient is calculated by identifying all prescribed ACH drugs, followed by adding up the scores of the substances (cumulative ACH burden). The resulting score helps identify patients at high risk of ACH-related ADEs and could provide an opportunity to perform interventions, such as discontinuation of a drug.

In our previous systematic review,⁵ we identified 19 ABSs with varying qualities.^{6–24} Some of the ABSs were developed by a systematic review and built on previously published scales,^{8,13,17,18,20} whereas other ABSs were derived from a serum radioreceptor anticholinergic activity (SAA) assay^{12,19} or are entirely based on computational receptor binding affinities.²⁴ Most of the ABSs also include the opinion of an expert committee, whose composition varies greatly. ABSs that were not based on simple lists but rather on equations, such as the Drug Burden Index (DBI),^{25,26} were excluded in this review.

Finally, some ABSs lack validation in clinical settings and others show contradicting results regarding the association with the investigated clinical outcomes, such as mortality. To our knowledge, no study has yet investigated all 19 ABSs in the same clinical setting. Hence, in this study, we aim to compare all published ABSs and evaluate their association with in-hospital mortality and length of stay (LOS).

2 | METHOD

2.1 | Study design and setting

We conducted a cohort study of patients hospitalised between January 2015 and December 2018 at a Swiss tertiary teaching hospital, which includes 360 beds. Our dataset is derived from patients' electronic health records (EHRs) (i.e., data routinely collected during the hospitalisation). This study was undertaken per the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.²⁷

2.2 | Ethics approval

For this study, a protocol was written and approved by the national ethics review committee (EKNZ Project ID: 2018-01000).

2.3 | Participants

We included patients 65 years and older, who were hospitalised for at least 48 h. Patients were excluded if they were outpatients or stayed in an intensive care unit (ICU) for more than 24 h because no EHRs are used in the ICU.

2.4 | Data collection

Demographic characteristics, laboratory values, medication intake and some variables from the nurse assessment tool ePA-AC²⁸ within the first 24 h upon admission were extracted for each patient from the hospital's clinical information system and cross-linked to the proper International Classification of Disease 10 (ICD-10) diagnosis codes. Comorbidities were grouped according to the Charlson comorbidity index based on the ICD-10 codes received at discharge using the R package *{comorbidity}*.²⁹ We grouped the following diseases: cancer and metastatic cancer (cancer), mild and moderate to severe liver disease (liver disease) and diabetes with and without chronic complications (diabetes). The coded comorbidity was carried forward in case of repeated hospitalisations of the same patient because we considered these mostly to be chronic conditions. Additionally, we grouped for all-cause delirium at admission or during hospitalisation using the following ICD-10 codes: F05.0, F05.1, F05.8, F05.9, F10.4, F11.4, F12.4, F13.4, F14.4, F15.4, F16.4, F17.4, F18.4 and F19.4.

The ePA-AC tool²⁸ is performed by nurses at entry and then every other day, systematically assessing information on cognition, care, mobility and nutritional status of patients. We used the self-care index (SPI), the Braden score and the nutrition deficiency score. An SPI score of 32 or more points means that patients can take care of themselves; a Braden score below 12 points is associated with a high risk of development of a decubitus and last a nutrition deficiency score with three or more points representing malnutrition. The variable polymedication stands for the amount of different drugs taken by a patient and was considered numerical.

In contrast to variables with high proportions of missing data, only those with more than 20% available data were considered. For categorical and binary variables, we

generated the potential category 'missing'. Table 1 summarises the patient characteristics of the dataset by using the R package *{tableone}*.³⁰

2.5 | Main outcome and measures

The exact date of death was identified from the hospital discharge note and coded as a binary variable. The LOS was calculated from the admission to the discharge date. Due to a skewed distribution of the LOS, we log-transformed the data, which were back-transformed to ease interpretation.³¹

2.6 | Exposure

We considered all drugs in single active ingredient and combination products administered within the first 24 h of hospitalisation. The extracted raw data did not always contain machine-readable information on the active ingredients of the ordered drugs, as a consequence of for instance nonstandardised free-text entries, some of them with misspellings, hampering comprehensive drug identification. Based on the Anatomical Therapeutic Chemical Classification System (World Health Organisation, Geneva, Switzerland), we mapped the medication orders to their active ingredients in a semi-automated process as described by Siebenhüner et al.³²

For every ABS, the cumulative ACH burden score was calculated using all 19 ABSs, which were identified and described in our systematic review.⁵ A list of all the drugs can be found in supporting information Table S1. Drugs not scored were assumed to have no ACH activity and received zero points. All but four ABSs used a 4-point grading system (0: no to 3: high).^{13,14,19,24} For the scale by Minzenberg et al.,¹⁹ 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 PI and CI were analysed separately. In the scale developed by Duran et al. (DS),¹³ high potency drugs received a score of three points, low potency drugs received a score of two points, drugs listed in Table 4 in Duran's publication received a score of one point and drugs in Annex Sublist 1 in this publication received a score of half a point. The Anticholinergic Activity Scale (AAS)¹⁴ was transformed as follows: four into three, three into two, two and one into one and zero remained zero. Finally, the Anticholinergic Toxicity Scale (ATS)²⁴ was not transformed because the scoring ranges between half a point and five points, which is very close to the scoring of other ABSs. We classified the patients into two or three groups of exposure using each scale, as follows: 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

Statistical analyses were performed using R version 3.6.2 and the integrated development environment R Studio.³³ The R functions and corresponding packages are denoted as function *{package}*.³⁴ To compare the characteristics of patients based on their ACH drug exposure, we used a Chi square test for categorical and dichotomous variables, for continuous variables with normal distribution a one-way test (three groups) or *t*-test (two groups) and in case of nonnormal distributions or unequal variance a Kruskal–Wallis test (three groups) or Mann–Whitney *U* test (two groups). The *p*-values calculated in this report assume a significance level of .05. We report the mean \pm the standard deviation or the median and interquartile range for continuous, and numbers with percentages for categorical variables.

To test for multicollinearity between the covariables, we calculated the variance of inflation factor (VIF) for each variable with *vif {car}*.³⁵ If variables have more than two degrees of freedom (Df), the generalised variance of inflation factor (GVIF) was calculated instead. Variables showing a $GVIF^{(1/Df)} > 10$ were excluded from the multi-variable analysis.

A logistic regression model was used with a logit-link function for the outcome of in-hospital mortality, and a linear regression was conducted for the log-transformed outcome of the LOS. For the LOS analysis, we excluded patients who died. We performed univariable and multi-variable analyses adjusting for covariables for both outcomes that were selected based on prior work.⁵ Since we fitted 19 models by simply exchanging the ABS predictor, we did not need to adjust for multiple testing.

Bearing in mind that our inclusion criterion of patients aged 65 years and older could be considered a rather young cut-off to study death unlike Kidd et al.,³⁶ who included much older patients exactly for this reason, we added a subgroup analysis for in-hospital mortality according to stratified age groups.

3 | RESULTS

A total of 130,105 patients 65 years and older were hospitalised for longer than 48 h from 2015 to 2018. After applying the inclusion and exclusion criteria, we identified 27,092 patients (Figure 1) with a mean age of 781 ± 7.7 years, of which 14,014 (51.7%) were women,

TABLE 1 Patient characteristics of the entire cohort

Patient characteristics	Overall (n: 27,092)
Died, n (%)	913 (3.4)
Length of stay (LOS), median days [IQR]	6.00 [4.00, 10.00]
Age, mean years (\pm SD)	78.08 (7.69)
Age, n (%)	
65–75 years	10,932 (40.4)
76–85 years	11,012 (40.6)
86–95 years	4958 (18.3)
>95 years	190 (0.7)
Female sex, n (%)	14,014 (51.7)
Department, n (%)	
Medical department	15,119 (55.8)
Surgical department	11,973 (44.2)
Hearing device, n (%)	
None	15,674 (57.9)
Hearing device	2976 (11.0)
Missing	8442 (31.2)
Visual aid, n (%)	
None	4956 (18.3)
Glasses or contacts	13,630 (50.3)
Missing	8506 (31.4)
Acute myocardial infarction, n (%)	1442 (5.3)
Congestive heart failure, n (%)	4751 (17.5)
Peripheral vascular disease, n (%)	3691 (13.6)
Cerebrovascular disease, n (%)	3462 (12.8)
Dementia, n (%)	2595 (9.6)
COPD, n (%)	3041 (11.2)
Rheumatoid disease, n (%)	798 (2.9)
Peptic ulcer disease, n (%)	542 (2.0)
Liver disease, n (%)	541 (2.0)
Diabetes, n (%)	5692 (21.0)
Hemiplegia, Paraplegia, n (%)	1232 (4.5)
Renal dysfunction, n (%)	6176 (22.8)
Cancer, n (%)	4625 (17.1)
Delirium, n (%)	1695 (6.3)
Self-care index, median [IQR]	39.00 [34.00, 40.00]
Braden, median [IQR]	22.00 [20.00, 23.00]
Nutrition deficiency score, median [IQR]	1.00 [1.00, 2.00]
Catheterisation, n (%)	7873 (29.1)
Surgery during stay, n (%)	8676 (32.0)
Polymedication, mean [\pm SD]	7.58 (3.84)
GFR [ml/min], median [IQR]	64.00 [45.00, 80.00]
Creatinine [μ mol/l], median [IQR]	87.00 [70.00, 115.50]

(Continues)

TABLE 1 (Continued)

Patient characteristics	Overall (n: 27,092)
Sodium [mmol/l], median [IQR]	138.00 [135.00, 140.00]
Potassium [mmol/l], median [IQR]	4.05 [3.80, 4.35]
ALAT [U/l], median [IQR]	20.00 [14.00, 35.00]
ASAT [U/l], median [IQR]	25.00 [20.00, 35.00]
CRP [mg/l], median [IQR]	12.00 [2.70, 56.00]
CRP [mg/l], n (%)	
<5	7884 (29.1)
5–10	2680 (9.9)
10–50	6070 (22.4)
>50	6116 (22.6)
Missing	4342 (16.0)
Temperature [°C], median [IQR]	36.55 [36.25, 36.90]
Systolic blood pressure [mmHg], mean (±SD)	134.14 (19.77)
Diastolic blood pressure [mmHg], mean (±SD)	71.89 (11.67)
BMI, mean (±SD)	26.10 (3.84)

Abbreviations: ALAT, alanine transaminase; ASAT, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; GFR, glomerular filtration rate; IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

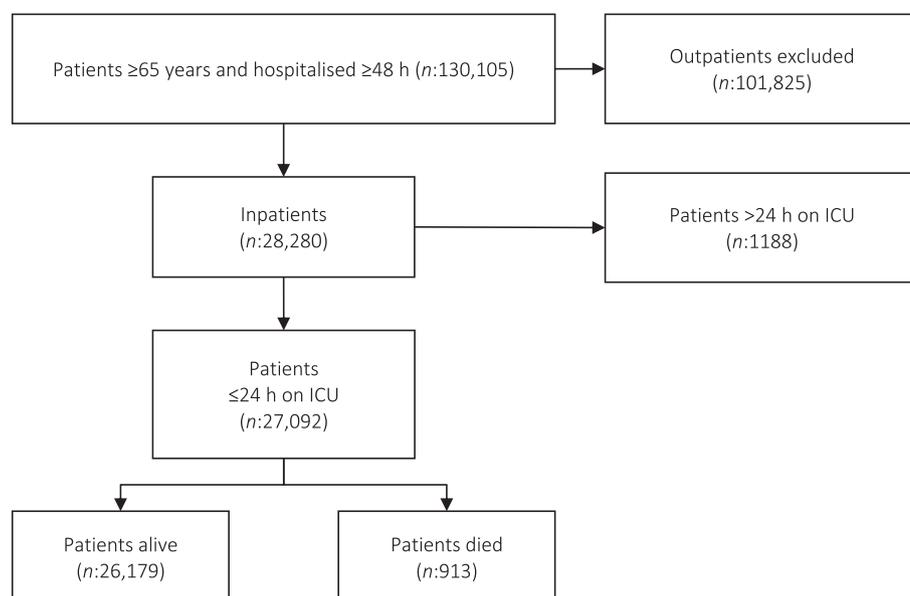


FIGURE 1 Flowchart of included and excluded patients

and the median LOS was 6 days. Out of these, 913 died during hospitalisation (3.4%). Overall, exposure to drugs with ACH properties depended on the ABS used to quantify the cumulative ACH burden: between 1370 patients (5.1%, measured with the ATS) and 17,035 patients (62.9%, measured with the German Anticholinergic Burden Scale [GABS]) were exposed to drugs with ACH properties. Further characteristics of the patients are depicted in Table 1. Patient characteristics divided by exposure for both approaches (binary and categorical)

with respect to the used ABS can be found in supporting information Tables S2 and S3, respectively.

The following variables contained missing values: systolic blood pressure (5.2%), diastolic blood pressure (5.2% missing), body temperature (13.8%), SPI (46.3%), Braden score (45.9%), nutrition deficiency score (58.3%), visual aid (31.4%), hearing device (31.2%), body mass index (BMI) (36.1%), glomerular filtration rate (GFR) (12.3%), creatinine (12.2%), sodium (12.4%), potassium (12.4%), alanine transaminase (ALAT) (73.1%), aspartate

transaminase (ASAT) (28.2%), C-reactive protein (CRP) (16.0%) and polymedication (10.0%). We did not detect any collinearity between the variables.

3.1 | Primary outcome mortality

Results of the binary and univariable analysis indicate that a high ACH burden score of three or more points was significantly associated with in-hospital mortality after applying all of the 19 ABSs. After adjusting for covariables, the found associations in all ABSs remained significant (Table 2). Summer's Class of Drug List (SCDL)

showed the largest effect size followed by the ATS and the Anticholinergic Drug Scale (ADS).

In the categorical analysis, all ABSs, except Cancelli's Anticholinergic Burden Scale (CABS) and Minzenberg's PI, exhibited a gradual increase in the odds of a higher ACH burden score. Again, all 19 ABSs from the binary analysis remained significantly associated when exposed to a high ACH burden score (three or more points) but in most cases were not significantly associated when comparing no burden (zero points) to low burden (half a point to less than three points). Only four scales, the Anticholinergic Risk Scale (ARS), the CABS, the ADS and the Anticholinergic Cognitive Burden Scale (ACB)

TABLE 2 Multivariable regression using the binary approach for both outcomes: in-hospital mortality and length of stay (LOS)

Scale	Mortality		LOS		Low <3 (n died (%))	High ≥3 (n died (%))
	OR	95% CI	Exp(B)	95% CI		
ABC ⁶	1.39	1.11–1.72	1.08	1.04–1.11	25,348 (778 (3.1%))	1744 (125 (7.2%))
AEC ⁷	1.49	1.17–1.87	1.00	0.96–1.03	25,512 (814 (3.2%))	1580 (99 (6.3%))
ACB ⁹	1.55	1.32–1.80	1.03	1.01–1.05	22,013 (630 (2.9%))	5079 (283 (5.6%))
AIS ⁸	1.58	1.37–1.82	1.07	1.06–1.09	19,343 (507 (2.6%))	7749 (406 (5.2%))
CABS ¹⁰	1.35	1.09–1.65	1.03	1.00–1.06	24,820 (770 (3.1%))	2272 (143 (6.3%))
Chew ¹²	1.37	1.12–1.66	1.12	1.09–1.15	24,534 (768 (3.1%))	2558 (145 (5.7%))
AAS ¹⁴	1.34	1.11–1.62	1.01	0.98–1.04	24,381 (748 (3.1%))	2711 (165 (6.1%))
ARS ²¹	1.92	1.50–2.42	1.01	0.97–1.05	25,821 (816 (3.2%))	1271 (97 (7.6%))
ACL ²²	1.53	1.23–1.88	1.12	1.09–1.15	24,979 (794 (3.2%))	2113 (119 (5.6%))
CrAS ¹⁵	1.85	1.57–2.18	1.12	1.10–1.14	23,319 (675 (2.9%))	3773 (238 (6.3%))
ADS ¹¹	2.13	1.80–2.51	1.16	1.13–1.19	23,919 (691 (2.9%))	3173 (222 (7.0%))
SCDL ²³	3.03	2.56–3.57	1.12	1.09–1.14	23,790 (677 (2.8%))	3302 (236 (7.1%))
PI ¹⁹	1.32	1.05–1.64	1.00	0.97–1.03	24,955 (791 (3.2%))	2137 (122 (5.7%))
CI ¹⁹	1.35	1.07–1.69	0.99	0.96–1.02	25,086 (795 (3.2%))	2006 (118 (5.9%))
GABS ¹⁸	1.51	1.31–1.74	1.08	1.06–1.10	18,586 (487 (2.6%))	8506 (426 (5.0%))
DS ¹³	1.86	1.61–2.14	1.11	1.09–1.13	19,302 (477 (2.5%))	7790 (436 (5.6%))
BAADS ²⁰	1.69	1.46–1.95	1.07	1.05–1.09	18,949 (473 (2.5%))	8143 (440 (5.4%))
KABS ¹⁷	1.65	1.42–1.91	1.08	1.06–1.10	21,416 (597 (2.8%))	5676 (316 (5.6%))
ATS ²⁴	2.22	1.72–2.84	1.00	0.96–1.04	26,137 (821 (3.1%))	955 (92 (9.6%))
DRS ¹⁶	1.66	1.43–1.93	1.11	1.09–1.13	21,398 (598 (2.8%))	5694 (315 (5.5%))

Note: Far-left column: individual ABS; two columns on the far right: absolute number of patients and percentage of prevalence of in-hospital deaths for each group. Multivariable analysis is adjusted for age, sex, dementia, delirium, congestive heart failure, hemiplegia/paraplegia, chronic obstructive pulmonary disease, rheumatic diseases, diabetes, liver disease, cancer, renal disease, cerebrovascular disease, acute myocardial infarction, peripheral vascular disease, peptic ulcer and categorical C-reactive protein. For the univariable analysis and analysis adjusted only for age and sex; see supporting information Tables S4.1 and S4.2. For LOS, the back-transformed estimate coefficient to the power of e is depicted as Exp(B) and can be interpreted as ABC Exp(B): 1.04, 4% longer hospitalisation stay.

Abbreviations: AAS, Anticholinergic Activity Scale; ABC, Anticholinergic Burden Classification; ACB, Anticholinergic Cognitive Burden Scale; ACL, Anticholinergic Loading Scale; ADS, Anticholinergic Drug Scale; AEC, Anticholinergic Effect on Cognition; AIS, Anticholinergic Impregnation Scale; ARS, Anticholinergic Risk Scale; ATS, Anticholinergic Toxicity Scale; BAADS, Brazilian Anticholinergic Activity Drug Scale; CABS, Cancelli's Anticholinergic Burden Scale; CI, Clinical Index; CrAS, Clinician-rated Anticholinergic Scale; DRS, Delirogenic Risk Scale; DS, Duran Scale; GABS, German Anticholinergic Burden Scale; KABS, Korean Anticholinergic Burden Scale; PI, Minzenberg's Pharmacological Index; SCDL, Summer's Class of Drug List.

demonstrated a significant association with increased in-hospital mortality when comparing no to low and no to high ACH burden while being adjusted for covariables (Table 3). The univariable and multivariable analyses adjusted to age and sex for both approaches are in supporting information Tables S4.1–S4.4.

The subgroup analysis stratified according to age groups revealed that there might be an effect modification leading to overestimation of the results (supporting information Table S4.5). Although in all age groups we found an association with increased in-hospital mortality, significance was lost with increasing age except when using newer ABSs and higher odds ratios were observed for patients in age group one (65–75 years) compared with the others.

3.2 | Secondary outcome LOS

In the binary approach, univariable analysis showed that a high ACH burden score of three or more points measured with 19 ABSs was significantly associated with a 9% to 33% prolonged LOS. After adjusting for covariables, 13 ABSs remained significantly associated and resulted in a 3% to 16% longer stay (Table 2). The strongest associations were observed for the ADS, followed by the SCDL, Anticholinergic Load Scale (ACL), Clinician-rated Anticholinergic Scale (CrAS) and Chew. In the categorical multivariable analysis, a gradual increase was observed in 11 ABSs. The univariable and multivariable analyses adjusted to age and sex are in supporting information Tables S4.1–S4.4.

4 | DISCUSSION

The ACH properties of drugs are a risk for ADEs in older patients. Therefore, numerous ABSs have been developed to quantify the cumulative ACH burden in a patient by scoring each substance from zero points (no ACH properties) to three points (high ACH properties) and thus guide clinicians in their evaluation of drug-related risk of adverse events.

4.1 | Primary outcome mortality

We demonstrate that a cumulative ACH burden score of three or more points in a patient measured by all 19 ABSs was significantly associated with in-hospital mortality. A reason for the small differences in the effect size between the scales could be the varying sample sizes (supporting information Tables S2 and S3) due to the different

number of drugs scored to have ACH properties. If an ABS scored only a few drugs with mostly two or three points, sample size in terms of exposure becomes more imbalanced and the association is stronger as seen with the SCDL and ATS especially in the categorical approach. Furthermore, while some ABSs were restrictive in scoring drugs with one point (i.e. the SCDL), others assigned this many times. This implies that when using such a scale, it is important to take the cumulative ACH burden to reach a high score (three points or more points). In all ABSs only one substance (amitriptyline) was scored unanimously with a score of three points. Other reasons could be the different countries and time points the ABSs were developed. The oldest scale (SCDL) was developed in 1978, and the newest (Brazilian Anticholinergic Activity Scale [BAADS]) was in 2019. Starting in 2013, six ABSs (DS, Delirogenic Risk Scale [DRS], Anticholinergic Impregnation Scale [AIS], GABS, Korean Anticholinergic Burden Scale [KABS] and BAADS) were published based on a systematic review on prior published scales compared with the ABSs from the early 2000s, which were primarily single studies using different methods for the scale development ranging from expert opinions and literature reviews to SAA. However, these newer ABSs did not improve the original ABSs much with respect to their association with in-hospital mortality.

In our previous review, we systematically assessed the quality of the ABSs.⁵ Regarding the scales with the best quality (ACB, DS, GABS and Anticholinergic Effect on Cognition [AEC]), all of them exhibited a significant association in the present study, whereas the ABSs with the lowest quality (SCDL) had the strongest association. This points to the conclusion that quality does not seem to play an important role.

The only scale standing out is the ATS,²⁴ which showed a strong result and for which this study is the first validation. The ATS uses a computational scoring approach considering the chemical structure of a substance, the off-target interactions and different muscarinic receptor subtypes and is completely objective. This approach seems good enough to identify all the substances scored with three points or more by other ABSs without taking into account clinical judgements or any pharmacodynamic characteristics. In the future, the ATS could potentially be used to study a specific ACH side effect affecting only one receptor subtype, because it differentiates between the muscarinic receptor subtypes. More studies using the ATS are warranted to confirm our findings.

Twenty-one previous cohort and case-control studies investigated the association of six ABSs (ACB, ADS DS, ARS, Chew and AEC) with mortality in the older population.^{5,36–56} However, these studies are not all comparable

TABLE 3 Multivariable regression using the categorical approach for both outcomes: In-hospital mortality and length of stay (LOS)

Scale	Mortality		LOS		Exposed (<i>n</i> died (%))
	OR	95% CI	Exp(B)	95% CI	
ABC⁶					
No burden	Reference				25,096 (781 (3.1%))
Low burden	0.60	0.25–1.21	0.97	0.88–1.06	252 (7 (2.8%))
High burden	1.38	1.10–1.71	1.03	0.98–1.09	1744 (125 (7.2%))
AEC⁷					
No burden	Reference				20,728 (611 (2.9%))
Low burden	1.13	0.95–1.34	1.00	0.97–1.03	4784 (203 (4.2%))
High burden	1.54	1.20–1.94	0.95	0.90–1.00	1580 (99 (6.3%))
ACB⁹					
No burden	Reference				15,993 (411 (2.6%))
Low burden	1.24	1.04–1.48	0.99	0.96–1.01	6020 (219 (3.6%))
High burden	1.66	1.40–1.96	0.97	0.94–0.99	5079 (283 (5.6%))
AIS⁸					
No burden	Reference				11,532 (295 (2.6%))
Low burden	1.03	0.85–1.24	0.99	0.97–1.01	7811 (211 (2.7%))
High burden	1.60	1.36–1.88	1.01	0.99–1.03	7749 (406 (5.2%))
CABS¹⁰					
No burden	Reference				23,444 (679 (2.9%))
Low burden	1.69	1.32–2.14	1.03	0.98–1.07	1376 (91 (6.6%))
High burden	1.45	1.17–1.78	0.97	0.92–1.02	2272 (143 (6.3%))
Chew¹²					
No burden	Reference				18,548 (535 (2.9%))
Low burden	1.06	0.90–1.25	1.02	1.00–1.05	5986 (233 (3.9%))
High burden	1.40	1.14–1.71	1.08	1.02–1.14	2558 (145 (5.7%))
AAS¹⁴					
No burden	Reference				21,777 (620 (2.8%))
Low burden	1.19	0.96–1.46	0.98	0.95–1.02	2604 (128 (4.9%))
High burden	1.39	1.14–1.68	0.98	0.94–1.02	2711 (165 (6.1%))
ARS²¹					
No burden	Reference				22,015 (639 (2.9%))
Low burden	1.27	1.06–1.52	0.97	0.95–1.00	3806 (177 (4.7%))
High burden	2.03	1.59–2.58	1.04	0.99–1.10	1271 (97 (7.6%))
ACL²²					
No burden	Reference				19,473 (603 (3.1%))
Low burden	1.02	0.86–1.21	1.02	1.00–1.05	5506 (191 (3.5%))
High burden	1.54	1.23–1.90	1.10	1.04–1.17	2113 (119 (5.6%))
CrAS¹⁵					
No burden	Reference				16,621 (470 (2.8%))
Low burden	1.08	0.90–1.28	1.02	1.00–1.04	6698 (205 (3.1%))
High burden	1.90	1.59–2.25	1.05	1.01–1.09	3773 (238 (6.3%))

(Continues)

TABLE 3 (Continued)

Scale	Mortality Multivariable		LOS		Exposed (<i>n</i> died (%))
	OR	95% CI	Exp(B)	95% CI	
ADS ¹¹					
No burden	Reference				16,306 (426 (2.6%))
Low burden	1.26	1.07–1.48	1.04	1.02–1.06	7613 (265 (3.5%))
High burden	2.32	1.94–2.77	1.08	1.04–1.13	3173 (222 (7.0%))
SCDL ²³					
No burden	Reference				17,518 (527 (3.0%))
Low burden	0.72	0.59–0.87	0.93	0.89–0.97	6272 (150 (2.4%))
High burden	2.78	2.34–3.30	1.11	1.07–1.15	3302 (236 (7.1%))
PI ¹⁹					
No burden	Reference				24,893 (789 (3.2%))
Low burden	2.46	0.40–8.15	1.06	0.85–1.31	62 (2 (3.2%))
High burden	1.32	1.05–1.64	0.97	0.93–1.00	2137 (122 (5.7%))
CI ¹⁹					
No burden	Reference				24,913 (788 (3.2%))
Low burden	1.06	0.44–2.18	1.05	0.93–1.18	173 (7 (4.0%))
High burden	1.35	1.08–1.69	0.96	0.92–0.99	2006 (118 (5.9%))
GABS ¹⁸					
No burden	Reference				10,057 (265 (2.6%))
Low burden	0.98	0.81–1.18	0.98	0.96–0.99	8529 (122 (2.6%))
High burden	1.49	1.27–1.77	1.00	0.98–1.03	8506 (426 (5.0%))
DS ¹³					
No burden	Reference				11,404 (281 (2.5%))
Low burden	0.92	0.76–1.11	0.99	0.98–1.01	7898 (196 (2.5%))
High burden	1.79	1.52–2.11	1.03	1.00–1.05	7790 (436 (5.6%))
BAADS ²⁰					
No burden	Reference				11,257 (276 (2.5%))
Low burden	0.97	0.80–1.17	1.00	0.98–1.02	7692 (197 (2.6%))
High burden	1.67	1.42–1.96	1.00	0.98–1.03	8143 (440 (5.4%))
KABS ¹⁷					
No burden	Reference				14,287 (366 (2.6%))
Low burden	1.16	0.97–1.38	1.01	0.99–1.03	7129 (231 (3.2%))
High burden	1.74	1.48–2.05	1.01	0.98–1.03	5676 (316 (5.6%))
ATS ²⁴					
No burden	Reference				25,722 (797 (3.1%))
Low burden	1.50	0.94–2.29	1.14	1.05–1.24	415 (24 (5.8%))
High burden	2.24	1.74–2.87	1.00	0.94–1.06	955 (92 (9.6%))

(Continues)

TABLE 3 (Continued)

Scale	Mortality Multivariable		LOS		Exposed (<i>n</i> died (%))
	OR	95% CI	Exp(B)	95% CI	
DRS ¹⁶					
No burden	Reference				13,523 (346 (2.6%))
Low burden	1.14	0.96–1.35	1.01	1.00–1.03	7875 (252 (3.2%))
High burden	1.75	1.48–2.07	1.04	1.01–1.07	5694 (315 (5.5%))

Note: Far-left column: individual ABS; two columns on the far right: absolute number of patients and percentage of prevalence of in-hospital deaths for each group. Multivariable analysis is adjusted for age, sex, dementia, delirium, congestive heart failure, hemiplegia/paraplegia, chronic obstructive pulmonary disease, rheumatic diseases, diabetes, liver disease, cancer, renal disease, cerebrovascular disease, acute myocardial infarction, peripheral vascular disease, peptic ulcer and categorical C-reactive protein. For the univariable analysis and analysis adjusted only for age and sex; see supporting information Tables S4.3 and S4.4. For LOS, the back-transformed estimate coefficient to the power of *e* is depicted as Exp(*B*) and can be interpreted as ABC Exp(*B*): 1.04, 4% longer hospitalisation stay.

Abbreviations: AAS, Anticholinergic Activity Scale; ABC, Anticholinergic Burden Classification; ACB, Anticholinergic Cognitive Burden Scale; ACL, Anticholinergic Loading Scale; ADS, Anticholinergic Drug Scale; AEC, Anticholinergic Effect on Cognition; AIS, Anticholinergic Impregnation Scale; ARS, Anticholinergic Risk Scale; ATS, Anticholinergic Toxicity Scale; BAADS, Brazilian Anticholinergic Activity Drug Scale; CABS, Cancelli's Anticholinergic Burden Scale; CI, Clinical Index; CrAS, Clinician-rated Anticholinergic Scale; DRS, Delirogenic Risk Scale; DS, Duran Scale; GABS, German Anticholinergic Burden Scale; KABS, Korean Anticholinergic Burden Scale; PI, Minzenberg's Pharmacological index; SCDL, Summer's Class of Drug List.

with ours. Out of them, five investigated postdischarge mortality,^{39,44,46,50,51} six reports focused on a special population with dementia,^{37,48,56} stroke,⁴² depression,³⁸ and palliative care patients⁵⁵ and another six studies used data of outpatients or nursing homes.^{40,41,43,47,49,54} Another two studies^{45,53} are similar in terms of using data from patients older than 65 years. However, Mangoni et al.,⁴⁵ finding no association with the ARS, additionally studied the impact of heat waves while Lu et al.⁵³ uses a national health insurance database (no association with ARS), which is not clearly distinguishing between inpatients and outpatients. The remaining two studies are comparable with ours.^{36,52} Both evaluated the association of the ACH burden at admission and in-hospital mortality in older patients, but only Lowry et al. used the inclusion criteria of 65 years and older.⁵² The researchers found that a unit increase in the ARS is significantly associated with in-hospital mortality. Kidd et al.³⁶ included patients older than 90 years and showed that the ACH burden measured with the ACB is not associated with in-hospital mortality. Our study reproduced the findings in terms of the significance of the ARS. Furthermore, our subgroup analysis confirmed a loss of significance with increasing age for in-hospital mortality. However, if we were to include only the 'frail' age groups three and four (>86 years), we would lose power and, furthermore, predicting mortality, especially drug-induced, would become difficult because this patient population is inherently closer to the end of life.

Results of the categorical analyses exhibit no significant association with higher in-hospital mortality when comparing no to low ACH burden, with the exception of the ACB, CABS, ARS and ADS. Whereas a score of three

or more points compared with zero points was associated with increased in-hospital mortality, which is in line with our observations of the binary approach. Therefore, a cumulative ACH burden score of three or more points seems to be a valid cut-off that can be used in clinical practice to determine whether it is necessary to change the current medication of a patient admitted to the emergency room using any of the ABSs.

4.2 | Secondary outcome LOS

A high cumulative ACH burden derived from 13 ABSs demonstrated a significant association with an increased LOS from 3% to 16%. The other ABSs exhibited no effect.

In the pre-existing literature, contradictory results with regard to LOS have been reported. Thus far, only Salahudeen et al.⁵⁷ comparing eight ABSs (Anticholinergic Burden Classification [ABC], ADS, CrAS, ARS, Chew, ACB, ACL, AAS) found a positive significant association with LOS in all scales, which is confirmed by our findings for six out of the eight ABSs (ABC, ADS, CrAS, Chew, ACB and ACL). Nevertheless, in comparison with our study, they used pharmacy claims data. Several other studies, which differ from our study in terms of patient selection, analysed only one ABS and found no significant results.^{45,46,50,58,59} Kidd et al.³⁶ and Lowry et al.⁵² also investigated LOS and were not able to demonstrate a significant association when using the ABC and ARS. Our study confirms the findings for the ARS. Additionally, we observed an increased LOS for the AIS, SCDL, GABS, DS, BAADS, KABS and DRS when

adjusted for covariables, which has not been previously shown. We hypothesise that the weaker association with LOS observed in this study compared with in-hospital mortality might have been confounded by other unidentified factors, such as delay in placement in a rehabilitation centre or in nursing home that might have led to longer hospital stays unrelated to patients' health status.

4.3 | Strengths

To our knowledge, this study is the first to investigate all 19 published ABSs, and the study population sample size was substantially larger than in previous studies. Adjusting for many comorbidities reduced the possible confounding. In addition to the medication list by entry, the free-text entries were mapped to their ingredients because the medication lists are often incomplete, and combinations were included as well.

4.4 | Limitations

This study has some limitations. One of the main limitations is its retrospective and single-centre study design. Furthermore, we did not consider the dosage of medication and route of administration or conduct a follow-up after discharge for the outcome mortality. However, most of the ABSs have also been developed without regard to the dosage applied in practice. In our dataset, we could have calculated the dosage taken by the patient, but constructing a weighting factor to incorporate this dosage in the cumulative ACH burden would be difficult, because doses of certain medications have large ranges (i.e. quetiapine) and each substance has its own half-life. In addition, some medications are given daily or have been taken before admission while others are given on demand. Unfortunately, this differentiation of medication was not possible in our dataset but could potentially be improved when linking it to pharmacy claims or insurance data. Lastly, possible drug–drug interaction and patients' genetic predisposition (slow/fast metaboliser) might hamper the bioavailability of medications with ACH properties. Finally, no ABSs were specifically developed for Switzerland, potentially leading to incomplete or incorrect scoring due to the different drugs available nationally. Another limitation of this study is that it only considered medication within 24 h of admission, which could change during the course of the hospital stay. However, knowing already at admission that the odds for in-hospital mortality are higher might give enough time to install preventive measures and substitute medications with a high ACH burden score.

5 | CONCLUSION

The ABC, ACB, AIS, Chew, ACL, CrAS, ADS, SCDL, GABS, DS, BAADS, KABS and DRS showed a significant association with both outcomes. This is not surprising because the SCDL was the groundwork for the CrAS, which was further developed to the ADS, which was then included in several newer scales based on systematic reviews, such as GABS, DS, BAADS, KABS and DRS. As newer ABSs incorporate older versions and show more consistent results in both outcomes and subgroup analysis, we recommend to use one of these scales. Yet, any other ABS could be used, as the main trigger of both outcomes is the cumulative ACH burden score of three or more points, considered a high burden. Discontinuation or substituting drugs with strong ACH properties during admission might be a targeted intervention to reduce in-hospital mortality and LOS. Nevertheless, with 19 ABSs to measure the ACH burden, it might be time to work on an internationally agreed standard.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. Presentation of work: GSASA Congress 2020 (25.1-26.11.2020), poster and oral presentation.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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