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ORIGINAL ARTICLE

Anti-cholinergic burden and patient related clinical outcomes in an emergency general surgical setting

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Anti-Cholinergic Burden;
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Length of hospital stay;
Change in destination;
Emergency surgery

Summary *Background/objective:* The impact of medications with anti-cholinergic properties on morbidity and mortality of unselected adult patients admitted to the emergency general surgical setting has not been investigated.
Methods: All cases were identified prospectively from unselected adult patients admitted to the emergency general surgical ward between May to July 2016 in a UK centre with a catchment population circa 500,000. Prescribed medication lists were ascertained from case notes and electronic medical records. Anti-Cholinergic Burden (ACB) was calculated from medication lists. Patients were categorised into three groups based on ACB; none (ACB score of 0); moderate (up to ACB score of two); high (ACB score more than two). The effect of increasing ACB on selected outcomes of 30- and 90-day mortality, hospital readmission within 30-days of discharge and increased length of hospital stay were examined using multivariable logistic regression models.
Results: The 452 patients had a mean age (SD) of 51.7 (±20.6) years, 273 (60.4%) patients had no ACB burden, 106 (23.5%) had a ACB burden of up to two; and 73 (16.2%) had an ACB burden of $>$ 2. Multivariable analyses showed no association between high ACB burden and 90-day

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(fully adjusted odds ratio [OR] 0.56 (95%CI 0.12—2.85); $P = 0.48$) and 30-day mortality (fully adjusted OR = 0.75 (95%CI 0.05—11.04); $P = 0.84$). A significant association was observed between moderate ACB burden and 30-day hospital readmission (fully adjusted OR = 2.01 (95%CI 1.09—3.71); $P = 0.03$).

Conclusions: Anti-cholinergic burden may be linked to hospital readmission in adults admitted to an emergency general surgical ward.

1. Introduction

The adverse effects associated with anti-cholinergic medication use have been well documented in older adults aged 65 and over in the medical and elective surgical settings.[1—4] Previous studies have reported the prevalence of anti-cholinergic use to be as high as 50% in older adults in the community, however, its prevalence in unselected acutely ill general surgical adults is unclear.[4,5] Medications with anti-cholinergic properties are used to treat many chronic conditions, including gastrointestinal diseases such as excessive gastric acid and intestinal motility disorders.[6]

Through competitively binding to central and peripheral muscarinic receptors, anti-cholinergic medications act through inhibiting the effects of the neurotransmitter acetylcholine (Ach), resulting in the relatively high side-effect profile.[7] The commoner side-effects of anticholinergic medications include constipation, dry mouth, dry eyes, urinary retention, falls and confusion.[8] The culminate effect of taking multiple anti-cholinergic medications can be estimated by the anti-cholinergic burden, which can be measured using tools such as the Anti-Cholinergic Burden Scale (ACB).[9—11] The ACB is the most validated expert based anti-cholinergic scale on adverse anti-cholinergic outcomes.[9] In patients who undergo abdominal surgery, studies have reported an association between anti-cholinergic medication use and post-operative complications such as paralytic ileus.[3]

However, more serious adverse effects have also been reported in older adults, such as mortality. In a meta-analysis of 11 studies, Ruxton and colleagues reported an association between having an ACB score and all-cause mortality (fully adjusted OR (95% CI) = 2.06 (95%CI 1.82—2.33), with a 106% increase in mortality for each additional point added to a patient's ACB in older adults.[2] Earlier studies have primarily focused on the effect of ACB in older adults, however, the potentially high prevalence of anti-cholinergic medication use in emergency surgical admissions, coupled with the high adverse effect profile of ACB, makes the investigation of ACB on acutely ill general surgical patients a pertinent issue. Consequently, we aim to investigate the association between having an ACB burden and clinical outcomes including: mortality; readmission; and length of stay.

2. Material/patients and methods

As part of the Older Persons Surgical Outcomes Collaboration (OPSOC) http://www.opsoc.eu, this prospective cohort study was conducted in Aberdeen Royal Infirmary, a tertiary referral centre for general surgery serving approximately half a million residents of North East of Scotland. In line with OPSOC methodology previously described, data were collected within the acute general surgical admissions setting for all patients consecutively admitted to the emergency general surgical ward throughout May to July 2016 and patients were followed for three months.[12]

Patients were excluded if they presented with the following conditions: vascular, urological, trauma and orthopaedics and neurological surgical emergencies, as they would have been admitted under specialist surgical teams. No other inclusion or exclusion criteria were used and data were collected for consecutive acute surgical admissions during the study period. Patients admitted to the acute general surgical setting in the UK vary in their presenting pathology. Most admissions relate to the gastrointestinal system i.e. appendicitis, diverticulitis, bowel obstruction or pancreato-biliary disease, but may also include minor surgical condition such as abscesses, and non-specific abdominal pain. In the UK, all patients admitted to the emergency general surgical department remain under the care of the general surgical team, regardless of whether they receieve an emergency surgical procedure. Patients with surgically related problems admitted under medical teams with outreach surgical team input or patients managed conservatively under the care of medical teams were not included.

3. Outcomes

The primary outcome was the relationship between ACB and mortality at 90- and 30-days. The secondary outcomes were ACB and readmission within 30-day post-discharge, and increased hospital length of stay.

4. Data collection

Data were recorded and stored in conjunction with local data management standard operating procedures. This study was deemed a service evaluation and did not require ethical approval. Only audit registration and approval within the Aberdeen Royal Infirmary was required and granted. Medications on admission were collected in one OPSOC site (Aberdeen Royal Infirmary) during the 2016 audit cycle with the view of assessing the link between ACB and patient related outcomes.

Using the Aging Brain Program's ACB scoring table (as shown in the Supplementary Table 1), each medication was assigned an ACB score and the total ACB burden was calculated for each patient as described by Myint *et al*. [10,13] In addition to the established anti-cholinergic medications, we also classed Prochlorperazine (or Chlorperazine) and Procyclidine as scoring 3 after consultation with opinion leaders in the field. Each patient's total score was categorised into one of the three groups depending on the sum of their total ACB score (none (ACB = 0); moderate (ACB = 1–2), high (ACB ≥ 3)) (see Supplementary Table 1 for the scoring system).

To characterise co-morbidity, we recorded baseline characteristics, recorded categorically, for the following; anaemia (Hb < 129 g/L), hypoalbuminaemia (albumin <35 g/L) and polypharmacy (≥5 medications on admission). Frailty was assessed using the seven-point Canadian Study on Health and Aging (CSHA) Clinical Frailty Scale (Supplementary Table 2).

All cases were prospectively identified and baseline data assessed on admission. Follow-up data were obtained via in-hospital electronic records at a later date. A continuous value was recorded, for the length of hospital stay (LOS), with days rounded up to the nearest whole day integer. The LOS was arbitrarily re-categorised for ease of interpretation for clinicians, into three dichotomised variables <7 and ≥7-days, <10 days and ≥10-days and <14 days and ≥14-day, which corresponded approximately with the 80th, 90st and 95th centile values of the LOS. Readmission within 30 day, mortality at 30- and 90-days were also collected. Following the standard definition for multi-morbidity throughout the literature, we defined multi-morbidity as the presence of ≥2 co-morbidies. We only specifically recorded the presence of co-morbidies such as DM, cardiac failure and dementia as they form the Charlson Co-morbidity Index, which have been shown to be an accurate predictor of poor outcomes such as one-year mortality.[14] The variables were selected on the basis that they are known predictors of surgical outcomes and grouped into four models in order to allow for observation of how related characteristics, when adjusted for, influenced our measured outcomes.

5. Statistical analysis

All analyses were performed using Statistical Package for Social Science (SPSS), version 24.0. Characteristics were compared by ACB category using ANOVA and Chi-squared test for continuous and categorical data respectively. Logistic regression models were constructed to examine the association between ACB as the predictor variable (with ACB score of 0 as the reference category) and dichotomised outcomes. In all logistic regression models, we conducted unadjusted data (model A), and made additional adjustments for age, sex, and admission from home (model B), with further incremental adjustment for receipt of an emergency operation, low albumin, low haemoglobin, high CRP, low eGFR (model C), and finally we adjusted for the frailty scale (model D). No formal sample size calculation was carried out due to the nature of the observational study design.

6. Results

Data were collected from 500 unselected adults admitted to the emergency surgical ward, with 48 patients excluded due to incomplete data, leaving a cohort of 452 patients (see Fig. 1). Almost a third of patients underwent an emergency operation (32.5%), with 44% of patients who received an emergency operation taking medications with anti-cholinergic properties. The characteristics of the sample by categories of total ACB (score 0, score 1–2, score ≥3) are presented in Table 1. Of 452 patients, 39.6% (179) were taking anti-cholinergic medications, while 60.4% (273) had ACB score 0, 23.5% (106) had ACB score 1–2, and 16.2% (73) had ACB score ≥3. When focussing only on adults aged ≥65, the prevalence of anti-cholinergic use was 53.8%. ACB scores ranged from 0 to 10 with the mean ACB score (SD) of our cohort being 0.97 (±1.6). The mean age (SD) was 51.7 (±20.6) years. Increase in age, multi-morbidity, polypharmacy and emergency operations were observed with increasing ACB score, whereas albumin, eGFR and haemoglobin levels decreased with increasing ACB.

39.2% (177) were male and 60.8% (275) were female, with a greater proportion of female patients with higher ACB scores. Using the frailty scale, the highest proportion of adults with ACB score 1–2 were "well." Meanwhile, the greatest proportion of adults with ACB score ≥3 were "well with treated co-morbid disease."

We found that the number of co-morbid diseases a patient had correlated significantly with higher ACB scores (Fig. 2). In the fully adjusted multivariate model, we found no association between ACB score 1–2 (1.30 (0.37–4.56); $P = 0.69$) or ACB score of ≥3 (0.56 (0.12–2.85); $P = 0.48$) compared to those with ACB score of 0 with regard to the primary outcome of 90-day mortality (Table 2). We similarly found no association between ACB and 30-day mortality.

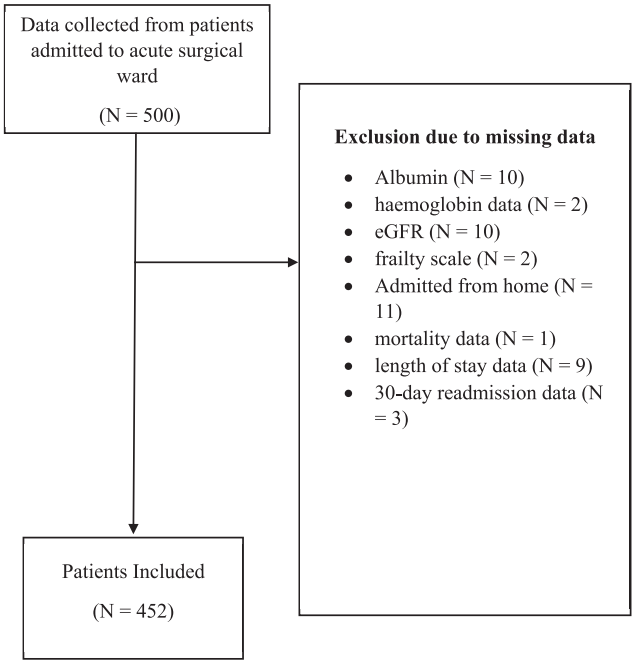

Figure 1 Flow chart describing reasons for exclusion.

Table 1 Patients' characteristics by anti-cholinergic burden score on admission (N = 452).

	ACB score 0 N = 273 (60.4%)	ACB score 1–2 N = 106 (23.5%)	ACB score ≥3 N = 73 (16.2%)	*P*
Characteristics				
Age (years)	46.87 (20.13)	61.31 (19.16)	55.73 (18.42)	**<0.001**
Sex				**0.002**
Male	119 (44)	43 (41)	15 (21)	
Female	154 (56)	63 (59)	58 (79)	
Admitted from home	267 (98)	101 (95)	67 (92)	**0.047**
Hypoalbuminaemia (g/l)	88 (32)	60 (57)	39 (53)	**<0.001**
Anaemia (g/l)	87 (32)	56 (53)	39 (53)	**<0.001**
eGFR≤60 (mL/min/1.73 m^2)	24 (9)	22 (21)	12 (16)	**0.005**
CRP				0.74
<10	123 (45)	42 (40)	27 (37)	
10–50	75 (27)	32 (30)	23 (32)	
>50	75 (27)	32 (30)	23 (32)	
Multimorbidity (≥2)	49 (18)	49 (46)	38 (52)	**<0.001**
Diabetes	17 (6)	9 (8)	16 (22)	**<0.001**
Dementia	6 (2)	4 (4)	3 (4)	0.56
Congestive cardiac failure	2 (1)	7 (7)	1 (1)	**0.002**
History of Falls	13 (5)	12 (11)	7 (10)	**0.054**
Depression	60 (22)	30 (28)	21 (29)	0.29
Visual Impairment	11 (4)	7 (7)	6 (8)	0.29
Hearing Impairment	21 (8)	18 (17)	4 (5)	**0.01**
Urinary Incontinence	1 (0)	5 (5)	5 (7)	**0.001**
Frailty Scale				**<0.001**
Very Fit	135 (49)	14 (13)	13 (18)	
Well	63 (23)	35 (33)	16 (22)	
Well with Treated Co-morbidities	44 (16)	24 (23)	23 (32)	
Apparently Vulnerable	22 (8)	21 (20)	11 (15)	
Mildly Frail	6 (2)	11 (10)	6 (8)	
Moderately Frail	2 (1)	1 (1)	4 (5)	
Severely Frail	1 (0)	0 (0)	0 (0)	
Polypharmacy	59 (22)	71 (67)	51 (70)	**<0.001**
Operation	106 (39)	27 (25)	14 (19)	**0.001**
Mortality at 90 days	6 (2)	7 (7)	3 (4)	0.11
Mortality at 30 days	4 (1)	3 (3)	3 (4)	0.35
Readmitted at 30 days	40 (15)	27 (25)	11 (15)	**0.038**
Length of Stay				
7 or more days	50 (18)	28 (26)	12 (16)	0.15
10 or more days	32 (12)	12 (11)	8 (11)	0.98
14 or more days	15 (5)	5 (5)	5 (7)	0.83

Bold values are statistically significant; p <0.05.
Values presented are mean (SD) for continuous data and number (%) for categorical data. P values were generated using a one-way ANOVA test for continuous variables and a chi square test for categorical variables.

ACB 1–2 was associated with 30-day readmission in our univariate (1.99 (1.15–3.45); $P = 0.01$) and fully adjusted logistic regression models (2.01 (1.09–3.71); $P = 0.025$). However, this association was lost in those with higher ACB scores (≥3). Our multivariate model showed no association between ACB and an increased length of hospital stay or a change in destination from home to not home (Table 3).

7. Discussion

Anti-cholinergic medication use is prevalent in emergency general surgical admissions with almost 40% of our cohort using at least one medication with anti-cholinergic properties. Patients with a greater co-morbidity burden were directly and positively associated with higher ACB. We found no association between ACB and mortality, length of hospital stay, or discharge destination of adult patients. However, a moderate ACB burden was associated with 30-day readmission. No association was found between ACB and readmission in those with the greatest ACB burden.

The existing literature on the association between ACB and outcomes focuses almost exclusively on older adults in community or medical settings. To the best of our knowledge, we are the first to report the prevalence of anti-cholinergic medication use in unselected adult patients

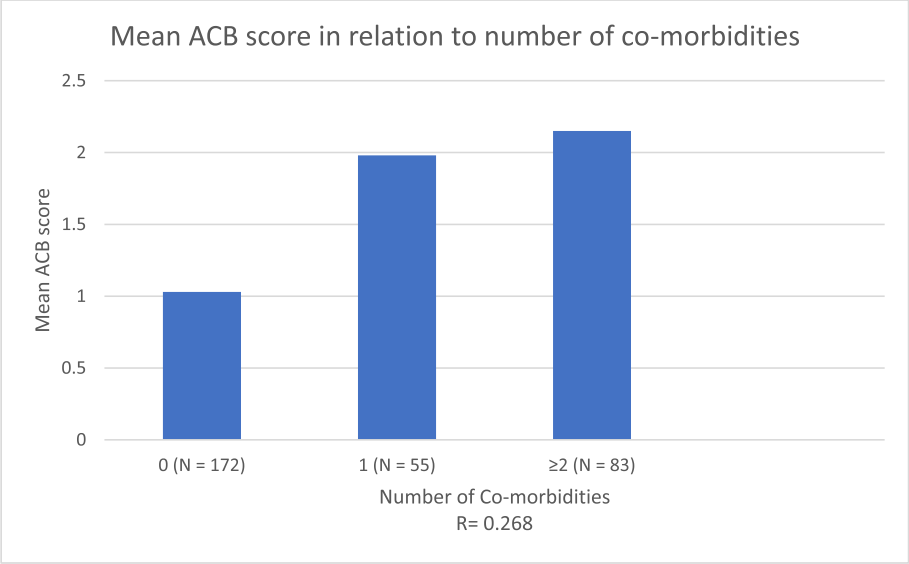

Figure 2 Comparing mean anti-cholinergic burden score with number of co-morbidities.

Table 2 Results of logistic regression analysis examining the association between anti-cholinergic burden (reference category = 0) and 90-day mortality, 30-day mortality and 30-day readmission.

Models	ACB 1–2 (N = 106)			ACB ≥3 (N = 73)		
	OR	95% CI	*P*	OR	95% CI	*P*
90-Day Mortality						
A	3.15	1.03–9.59	**0.044**	1.91	0.47–7.82	0.37
B	1.85	0.57–5.99	0.30	1.28	0.29–5.63	0.74
C	1.45	0.42–4.96	0.55	0.82	0.18–3.80	0.80
D	1.30	0.37–4.56	0.69	0.56	0.12–2.85	0.48
30-Day Mortality						
A	1.96	0.43–8.90	0.38	2.88	0.63–13.18	0.17
B	0.84	0.17–4.17	0.84	2.54	0.45–14.17	0.29
C	0.62	0.06–6.67	0.69	1.33	0.13–13.38	0.81
D	0.56	0.04–7.18	0.65	0.75	0.05–11.04	0.84
30-Day Readmission						
A	1.99	1.15–3.45	**0.014**	1.03	0.50–2.13	0.93
B	2.24	1.25–4.02	**0.007**	1.11	0.53–2.34	0.78
C	2.15	1.17–3.93	**0.013**	1.12	0.52–2.36	0.79
D	2.01	1.09–3.71	**0.025**	0.99	0.46–2.16	0.99

Bold values are statistically significant; p <0.05.
Model A: Unadjusted.
Model B: Age, Sex, Admitted from Home.
Model C: B + Operation, Hypoalbuminemia, Low Haemoglobin, CRP, eGFR.
Model D: C + Frailty scale.

Table 3 Results of logistic regression analysis examining the association between anti-cholinergic burden (reference category = 0) and length of stay (LOS); 7 days or more, 10 days or more, 14 days or more and change in destination from home to not home.

Models	ACB 1–2 (N = 106)			ACB ≥3 (N = 73)		
	OR	95% CI	*P*	OR	95% CI	*P*
LOS; 7 days or more						
A	1.60	0.94–2.72	0.08	0.88	0.44–1.75	0.71
B	1.04	0.59–1.86	0.89	0.60	0.28–1.28	0.19
C	1.19	0.62–2.28	0.60	0.64	0.28–1.49	0.30
D	1.14	0.59–2.20	0.69	0.60	0.26–1.41	0.24
LOS; 10 days or more						
A	0.96	0.48–1.95	0.91	0.93	0.41–2.11	0.86
B	0.58	0.27–1.26	0.17	0.59	0.24–1.47	0.26
C	0.61	0.26–1.42	0.25	0.64	0.24–1.70	0.37
D	0.60	0.25–1.39	0.23	0.61	0.23–1.65	0.33
LOS; 14 days or more						
A	0.85	0.30–2.40	0.76	1.27	0.44–3.60	0.66
B	0.44	0.14–1.33	0.14	0.96	0.31–3.00	0.95
C	0.44	0.13–1.54	0.20	1.28	0.37–4.43	0.69
D	0.44	0.13–1.52	0.19	1.20	0.34–4.27	0.77
Change in Destination from Home to not Home						
A	0.86	0.17–4.31	0.85	1.25	0.25–6.34	0.79
B	0.38	0.07–2.14	0.27	1.72	0.28–10.73	0.56
C	0.45	0.07–3.00	0.41	1.84	0.26–12.87	0.54
D	0.46	0.07–3.15	0.43	1.72	0.23–12.67	0.59

Model A: Unadjusted.
Model B: Age, Sex, Admitted from Home.
Model C: B + Operation, Hypoalbuminemia, Low Haemoglobin, CRP, eGFR.
Model D: C + Frailty scale.

admitted to the emergency general surgical ward. Whilst previous reports from 2009 have estimated the prevalence of anti-cholinergic medication use in only older adults in the community setting to be as high as 50%, our study found that the prevalence of anti-cholinergic use in unselected adults in emergency general surgical admissions to be almost 40%.[4] This may suggest that anti-cholinergic medication use is on the rise which is likely a consequence of increasing life expectancy and management of more complex patients living with a combination of co-morbid diseases.[15] This is supported by our findings (Fig. 2) which

show that the average ACB a patient had, positively correlated with the number of co-morbidities they were living with. Subsequently, as the use of anti-cholinergic medication may continue to rise, better understanding of their impact on surgical outcomes requires further investigations.

We observed that patients with a high ACB were less likely to undergo an emergency operation (Table 1). Consequently, in order to identify whether this finding was due to more co-morbidities in high ACB patients, we compared receipt of an emergency operation in moderate ACB and high ACB patients with increasing co-morbidities (Fig. 3). Our findings show that patients with high ACB and no co-morbidities were less likely to require an emergency operation than patients with high ACB and the presence of co-morbidities. This is likely due to patients taking medications to treat a non-surgical condition e.g. medications used to treat a patient with an overactive bladder are likely to score highly in ACB, yet such patients may not require an emergency operation for a gastrointestinal related condition.

We found no association between ACB and mortality. In a large cohort study of 21,636 community dwelling participants, aged between 40 and 79 years of age, Myint and colleagues observed that higher ACB scores were associated with mortality, with a mean follow up of 14.9 years.[13] Similarly, Fox and colleagues found an association between ACB and mortality at 2 years, 12, 423 participants.[16] Subsequently, our cohort consisted of only 452 patients and studies which have found an association between ACB and mortality tend to have a larger cohort, thus our study is likely to be underpowered.[12,16–18] However, given the observational nature of our study, a formal power analysis was not appropriate. Earlier studies have reported the relative deterioration of the central cholinergic system as a consequence of the aging process which increases the sensitivity of older patients to blockade of muscarinic receptors.[11,19] Therefore, it may be the case that ACB is only associated with mortality in older patients resulting from the combination of older people tending to have higher ACB scores, which we have shown to be positively correlated with co-morbidities, whilst also having a greater sensitivity to anti-cholinergics due to the deterioration of their cholinergic system. Nevertheless, in a systematic review of nine studies, most of the studies found no association between anti-cholinergics and mortality, however, Fox and colleagues concluded that the association was inconclusive, as a number of the studies had inadequate follow -up periods.[7,20,21]

Increased length of hospital stay and hospital readmissions are not only associated with poor patient outcomes, but they are also costly and resource consuming.[22,23] Although, previous studies have found an association between ACB and increased length of hospital stay in older patients, our study found no association between ACB and increased length of stay in adults, which is likely due to the relatively young age of our cohort.[24,25]

Nevertheless, at moderate ACB scores (1—2), we observed an association between ACB and 30-day hospital readmission. This finding is consistent with earlier reports which focused on the association between ACB and 30-day readmission in older adults, however we are the first to report this association in adults.[26,27] Nonetheless, this association was lost with a higher ACB score. This may be explained by the fact that patients with higher ACB tended to be older persons and likely to have healthcare arrangements which accommodate for the management of these patients in the community. Meanwhile, patients with a lower ACB tend to be younger therefore may not have such arrangements in place, thereby resulting in increased likelihood of 30-day hospital readmission.

Our study has a number of limitations. Firstly, as a result of the non-randomised study design, caution ought to be used when interpreting our findings. The follow -up period for measurement of mortality was only 90-days and may not be long enough to capture morality association with increased ACB burden. We did not have data on perioperative complications and therefore we were unable to observe any potential association between ACB and perioperative complications. Furthermore, we did not have

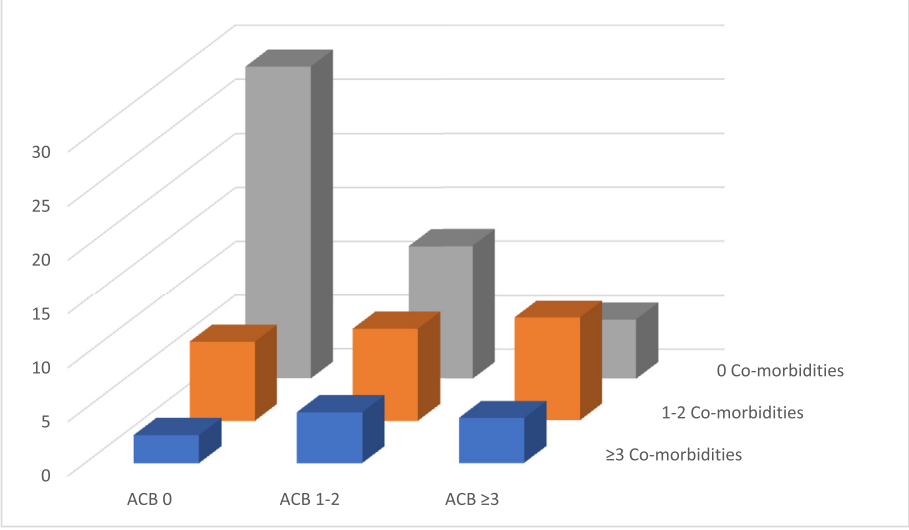

Figure 3 The proportion of patients undergoing an emergency operation comparing ACB category with increasing co-morbidities.

information on reason for hospital readmission, therefore we were unable to assess whether readmission could be explained by ACB. We recognise that a separate analysis including only patients who underwent an emergency operation would have been useful, due to relatively smaller sample receiving an emergent operation (n = 147), we decided not to conduct such analysis as this could potentially lead to type II error. While we were able to control for some markers of severity of acute illness such as anaemia, hypalbuminaemia and C-reactive protein level, since patients admitted in emergency setting are often complicated with Systemic Inflammatory Response Syndrome (SIRS) reactions, future work should include the use of clinical scores such as the Quick Sepsis Related Organ Failure Assessment (qSOFA) in their analysis in order to adequately accounted for sepsis.

Meanwhile, strengths of our paper include the use of a detailed and accurate medication lists extracted from electronic medical records. Additionally, patient data was collected for all consecutive adult admissions to the general surgical ward without selection. It is foreseeable that the patients who underwent an operation may be exposed to higher anti-cholinergic burden and future investigations should also focus on this patient population.

In conclusion, anti-cholinergic medication use is prevalent in unselected adult patients admitted to the emergency general surgical setting, with almost 40% of patients being prescribed at least one anti-cholinergic medication. We observed that whilst patients with a high ACB were less likely to receive an emergency operation, patients with a moderate ACB were associated with 30-day hospital readmission. We encourage further research into the association between anti-cholinergic medication use and outcomes in emergency surgical admissions perhaps focusing on older people and those who undergo operation.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.10.005.

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