Abstract

Background: Repeated hospital admissions are prevalent in older people. The role of medication in repeated hospital admissions has not been widely studied. The hypothesis that medication-related risk factors for initial hospital admissions were also associated with repeated hospital admissions was generated.

Objectives: To examine the association between medication-related risk factors and repeated hospital admissions in older people living with frailty.

Method: A retrospective case-control study was carried out with 200 patients aged ≥75 years with unplanned medical admissions into a large teaching hospital in England between January and December 2015. Demographic, clinical, and medication-related data were obtained from review of discharge summaries. Statistical comparisons were made between patients with 3 or more hospital admissions during the study period (cases) and those with 2 or fewer admissions (controls). Regressions were performed to establish independent predictors of repeated hospital admissions.

Results: Participants had a mean age of 83.8 years (SD 5.68) and 65.5% were female. There were 561 admission episodes across the sample, with the main reasons for admissions recorded as respiratory problems (25%) and falls (17%). Univariate logistic regression revealed five medication-related risks to be associated with repeated hospital admissions: Hyper-polypharmacy (defined as taking ≥10 medications) (OR 2.50, $p< 0.005$); prescription of potentially inappropriate medications (PIMs) (OR 1.89; $p<0.05$); prescription of a diuretic (OR 1.87; $p<0.05$); number of high risk medication (OR 1.29; $p<0.05$) and the number of 'when required' medication (OR 1.20; $p<0.05$). However, the effects of these risk factors became insignificant when comorbid disease was adjusted for in a multivariable model.

Conclusion: Medication-related risk factors may play an important role in future repeated admission risk prediction models. The modifiable nature of medication-related risks factors highlights a real opportunity to improve health outcomes.

Key words: repeated hospital admissions, prediction model, polypharmacy, medication risks, potentially inappropriate medication.

Title:

Medication-related risk factors and its association with frequent admissions in frail elderly: a case control study.

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Background

Older people living with frailty often experience frequent transitions of care due to high hospital admission rates.[1] Many older adults are living with at least two long-term conditions (multimorbidity)[2], which require multiple medications to manage these conditions.[3] Patients living with frailty experience higher levels of adverse drug events due to a decline in physiological reserves.[4] Hospital readmission rate is often used as an indicator of health system performance [5], and there is increasing evidence that hospital readmission is linked to worse patient outcomes.[6]

In the UK, emergency hospital readmission is defined as any repeated admission to hospital within 30 days of discharge.[7] This definition is used for the purpose of financial penalty for the National Health Service (NHS) in the UK. The desired outcome for this study is to examine the phenomenon of repeated hospital admissions in a longitudinal time period. This is important for the cohort of older people living with frailty as many of these patients are subjected to polypharmacy and are living with multi-morbidities. Therefore, their medical management is complex and the reason for admission may not always be immediately evident or attributable to a single disease state.[8] In addition, repeated hospital admissions affect the quality of life and patient satisfaction; and may reduce the quality of transitional care experienced.

Previous research has shown that medication can increase the risk of hospital admissions.[9] Therefore, we hypothesised that medication-related risk factors known to be associated with admissions, could be associated with repeated hospital admissions (RHAs) in the frail elderly. In 2013, it was estimated that emergency readmission cost the NHS approximately £2.4 billion a year.[10] The financial and clinical implications of hospital readmissions have prompted the development of predictive tools to identify individuals at risk of readmission.[11] More importantly, predictive risk tools provide an opportunity for clinicians to alter existing risk factors to mitigate such risks.[12] However, medications are often not included as a predictor in these tools, and could be an important modifiable risk factor which warrants further exploration. The aim of this research was to examine the association between medication-related risk factors and RHAs in frail elderly patients.

Method

Data source

Data for this study were obtained from the electronic discharge summary records of a large teaching hospital in Sheffield, South Yorkshire, which serves a population of approximately 1.7million people. Electronic discharge summaries contain demographic and clinical information including discharge medication lists.

Sample

A retrospective unmatched case-control method was used to approach routine data collected at the hospital between January and December 2015, from which two groups of frail elderly patients were identified and compared. The participants' frailty was not assessed directly as frailty was often not coded on hospital records and discharge summaries. Instead, we considered age and number of hospital admissions per year as proxies for 'frailty' in accordance with the Edmonton Frail Scale.[13] Group A (cases) included patients aged ≥ 75 years with more repeated hospital admissions (at least 3 during the study period) and Group B consisted of patients aged ≥ 75 years with fewer repeated hospital admission (less than 3 admissions). The data were extracted from discharge summaries of 200 randomly selected patients. 100 patients were randomly selected from 838 patients for Group A, and 100 from 8933 patients for Group B. Random selection was carried out using an online random number generator.[14] We only considered admissions that were unplanned and medical in nature, excluding elective and surgical admissions. Additionally, we excluded admissions to psychiatry and oncology services.

Measurements

Demographic data such as age, sex, and marital status were extracted. The number of co-morbidities were extracted from records of patients' histories and recorded as a simple count of long term conditions. Socioeconomic status was estimated using neighbourhood level Index of Multiple Deprivation (IMD).[15] Data for medication-related risks were obtained from the second unplanned admission in the year for Group A, and first unplanned admission of the year for Group B. This was to ensure consistency across the sample: everyone in Group A had an admission before and after their second admission; everyone in Group B had a first admission. Risks recorded included:

- Number of medicines on discharge;
- Prescription of high risk medicine(s)[16], which included: non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelets, antiepileptics, hypoglycaemics, diuretics, inhaled corticosteroids, cardiac glycosides, beta-blockers and anticoagulants (including direct acting oral anticoagulants);
- Presence of potentially inappropriate medicine (PIM) according to Table 2 of the Beer's Criteria[17];
- Medication changes (during hospital stay, as outlined on discharge summary) during second (group A) or first hospital admission (Group B)[18];
- Whether the patient received supported discharge
- Whether the patient received any multi-compartment aid (MCA) to use on discharge[19].

The number of medications on discharge was counted and participants assessed for hyper-polypharmacy (taking at least 10 medications). This definition is consistent

with Gnjidic et al.[20] whilst a common definition of polypharmacy as 5 or more medications [21] was not appropriate for this sample because most of the participants (96%) were taking at least 5 medications.

PIM and high risk medicines were both recorded muly (yes/no) and as a count. Discharge destination was extracted from discharge summaries and coded as 'discharged to home' (discharged directly home with no additional care facilities) or 'supported discharge' (discharged to residential care homes, intermediate care services or with domiciliary care packages).

Ethical approval was not required as this was carried out as part of a service evaluation project at the Trust using routine data. All data were collected by one investigator, who had normal access to the data, and was subsequently anonymised to ensure confidentiality of the data.

Statistical analyses

Between groups comparisons (cases vs controls) were carried out using a chi-squared test for categorical variables and t-test for continuous variables (data was normally distributed). Subsequently, univariate and stepwise multivariable logistic regression modelling was undertaken to identify independent predictors of RHAs as well as the predictive value of the overall model. For a variable to be included in the multivariable model, the Wald test should be significant at the level of $p<0.05$ in single variable regression. Further, odds ratios (and 95% confidence intervals) were reported for each model variable. A multi-variable regression model was used to identify independent predictors of RHAs. Single variables were included in the model by strength of association defined by p-value and application of the logistic model rule of thumb of a minimum of 10 events per predictor variable (EPV).[22] To enhance the clinical utility of any subsequent risk prediction tools developed, variables available at the point of admission were included. Some important variables such as number of discharge medication and supported discharge, were not available at the point of admission but were included due to their significance. We carried out collinearity diagnostics on the regression model variables and found the collinearities among the predictors to be low. All statistical tests were carried out using SPSS version 22.

Results

The demographics of the patients are presented in Table 1. While this case control study did not apply the principles of 'matching', demographic characteristics of the two groups of patients were not significantly different.

Participants in the sample had a mean age of 83.8 years (SD 5.68), were predominantly female (65.5%) and were commonly living alone (64%). Patients

living in the most deprived areas had higher RHAs than those not living in the most deprived areas (OR = 1.88; 95% CI 1.04 – 3.40; Table 2).

Table 1 Descriptive analysis of sample characteristics and variables

Variables	Overall	Higher Repeated admissions group (A)	Lower repeated admissions group (B)	Chi-square or t-test value	p-value
Age (years) Mean (SD)	83.8 (5.68)	83.6 (5.67)	83.9 (5.71)	-0.397	0.692
Sex					
Female	131(65.5%)	70 (70%)	61 (61%)	1.792	0.181
Male	69 (34.5%)	30 (30%)	39 (39%)		
Living with a spouse					
Yes	72 (36%)	33 (33%)	39 (39%)		
No	128 (64%)	67 (67%)	61 (61%)	0.781	0.377
Deprivation index					
Unclear (out of area)	8 (4%)	3 (3%)	5 (5%)		
Least deprived	55 (27.5%)	25 (25%)	30 (30%)	4.55	0.208
Moderately deprived	69 (35%)	31 (31%)	38 (38%)		
Most deprived	68 (34%)	41 (41%)	27 (27%)		
Co-morbidities (number of) Mean (SD)	4.84 (2.35)	5.79 (2.29)	3.89 (2.01)	6.231	0.000
Length of stay (days) Mean (SD)	10.37 (11.95)	8.78 (9.36)	11.96 (13.95)	-1.893	0.060
Discharge destination					
Home	148 (74%)	83 (83%)	65 (65%)	8.420	0.004
Supported discharge	52 (26%)	17 (17%)	35 (35%)		
Hyper-polypharmacy (≥ 10 medication)					
Yes	125 (62.5%)	73 (73%)	52 (52%)		
No	75 (37.5%)	27 (27%)	48 (48%)	9.408	0.002
Number of 'when required' medication Mean (SD)	1.75 (1.58)	1.97 (1.71)	1.52 (1.42)	2.023	0.044
Medication changed during hospital stay?					
Yes	156 (78%)	78 (78%)	78 (78%)		
No	44 (22%)	22 (22%)	22 (22%)	0.000	1.000

Variables	Overall	Higher Repeated admissions group (A)	Lower repeated admissions group (B)	Chi-square or t-test value	p-value
Presence of high risk medication?					
Yes	171 (85.5%)	89 (89%)	82 (82%)		
No	29 (14.5%)	11 (11%)	18 (18%)	1.976	0.160
High Risk Medication Class					
NSAIDs	2 (1%)	2 (1%)	0 (0%)	2.020	0.155
Antiplatelets	84 (42%)	44 (44%)	40 (40%)	0.328	0.567
Anti-epileptics	29 (14.5%)	16 (16%)	13 (13%)	0.363	0.547
Hypoglycaemics	18 (9%)	11 (11%)	7 (7%)	0.977	0.323
Diuretics	83 (41.5%)	49 (49%)	34 (34%)	4.634	0.031
Inhaled corticosteroids	50 (25%)	30 (30%)	20 (20%)	2.667	0.102
Cardiac glycosides	26 (13%)	14 (14%)	12 (12%)	0.177	0.674
Beta-blockers	81 (40.5%)	44 (44%)	37 (37%)	1.017	0.313
Anti-coagulants	57 (28.5%)	31 (31%)	26 (26%)	0.613	0.434
Number of high risk medication class					
Mean (SD)	2.15 (1.45)	2.41 (1.46)	1.89 (1.39)	2.574	0.011
Presence of PIM?					
Yes	66 (33%)	40 (40%)	26 (26%)		
No	134 (67%)	60 (60%)	74 (74%)	4.432	0.035
Number of PIMs					
Mean (SD)	0.4 (0.64)	0.5 (0.70)	0.3 (0.56)	-2.225	0.027

NSAIDs: Non-Steroidal Anti-inflammatory Drugs; PIM: Potentially-Inappropriate Medication;

Admission-level characteristics

The reasons for admission were based on presenting complaints documented on discharge summary for each admission. Of the 200 patients, there were 561 admissions with available information on presenting complaints over the course of 12 months. The most common reasons for admission were consistent across both groups of patients. These were: respiratory problems (including respiratory tract infection and exacerbation of chronic pulmonary disease) (n=140; 25%); fall (n=97; 17.3%); cardiovascular problems (including angina, heart failure and blood pressure problems) (n=76; 13.5%); and gastrointestinal problems (n=40; 7.1%).

Medication-related risks

Several medication-related risk factors were more prevalent in the RHAs group: number of comorbidities, supportive discharge, number of medication at discharge,

hyper-polypharmacy (≥ 10 medications), number of 'when required' medication, prescribed a diuretic, and prescribed a potentially inappropriate medication (PIM). The proportion of participants with: polypharmacy (≥5 medications), undergoing medication changes, or were prescribed a high risk medicine, were similar in both groups.

Single variable logistic regression revealed five medication-related risk factors that were associated with statistically significant increased odds of RHAs. Hyper-polypharmacy (≥ 10 medications) increased the odds of RHAs by 2.5 times (95% CI 1.38 – 4.51; p=0.002); along with prescription of potentially inappropriate medications (PIMs) in accordance with Beers Criteria [17] (OR 1.89; 95% CI 1.04 – 3.46; p=0.036), and number of 'when required' medication (OR 1.20; 95% CI 1.00 – 1.45; p=0.047). The most common PIMs used by patients within the study were amitriptyline (5.5%), solifenacin (5.5%), doxazosin (4%) and tamsulosin (4.5%). Whilst the dichotomous outcome of being prescribed a high risk drug (of any drug group) was not associated with RHAs, a cumulative effect of prescribing high risk drugs did exist with a 29% increase in the odds of RHAs with every additional high risk drug prescribed (OR 1.29; 95% CI 1.06 – 1.58). In addition, diuretic prescription in particular was associated with RHAs (OR 1.87; 95% CI 1.06 – 3.30).

Table 2: Results of single variable logistic regression (n=200) evaluating odds of RHA with each variable; listed in descending order of strength of association by p-value (strongest association at the top).

Variable	Odds ratio	95% CI	p-value
Number of comorbidities	1.50	1.29 – 1.74	0.000
Hyper-polypharmacy ≥10 medications	2.50	1.38 – 4.51	0.002
Discharge to home	2.63	1.35 – 5.11	0.004
Prescription of each additional high risk drug	1.29	1.06 – 1.58	0.012
Prescribed diuretics	1.87	1.06 – 3.30	0.032
Presence of PIM*	1.89	1.04 – 3.46	0.036
Deprivation index Most deprived	1.88	1.04 - 3.41	0.038
Number of PRN medication*	1.20	1.00 – 1.45	0.047
Length of stay (days)	0.98	0.95 – 1.00	0.068
Prescribed inhaled corticosteroids	1.71	0.90 – 3.29	0.104
Presence of high risk drugs	1.78	0.79 – 3.98	0.163
Gender (female)	1.49	0.83 – 2.68	0.182
Living with spouse	0.77	0.43 - 1.38	0.377
Use of compliance aid	1.16	0.63 – 2.17	0.635
Age on admission	0.99	0.94 – 1.04	0.690

*PRN: 'when required'; PIM: Potentially Inappropriate Medication as defined by modified-Beers Criteria.

Table 3: Multivariable logistic regression (n=200)

Variable	Odds ratio	95% CI	p-value
Number of comorbidities	1.512	1.274 – 1.794	0.000
Discharged to home	2.235	1.019 – 4.898	0.045
Living in the most deprived area(s)	1.841	0.916 – 3.700	0.087
Prescribed potentially inappropriate medicine(s)	1.795	0.876 – 3.677	0.110
Female	1.631	0.820 – 3.246	0.163
Number of PRN drugs	1.127	0.896 – 1.417	0.309
Number of high risk drugs	0.871	0.634 – 1.198	0.396
Prescribed diuretic(s)	1.424	0.614 – 3.302	0.411
Hyper-polypharmacy (≥10 meds)	1.057	0.467 – 2.394	0.894
Age on admission	0.997	0.941 – 1.056	0.922

The multivariable logistic regression model is presented in Table 3. After controlling for age, sex, deprivation index, discharge destination and comorbidities, none of the medication-related variables significantly predicted RHAs. The multivariable logistic regression model indicated that number of comorbidities and being discharged to home (without support) were significant predictors of RHAs. There was a greater than 50% increased odds of RHAs with the presence of each comorbid condition (95% CI 1.27 – 1.79), and a more than 2-fold increased odds of RHAs when patients were discharged directly home with no additional care facilities (95% CI 1.02 - 4.90). Whilst being prescribed a PIM potentially increased the odds of RHAs by nearly 80%, this increase was not statistically significant (OR 1.80; 95% CI 0.88-3.68; p=0.110). This regression model had a chi-square of 52.48 (DF=10) (p<0.001), with model predictors "explaining" 30.8% of the variability of frequency of RHAs (Nagelkerke pseudo-R^2 = 0.308). The Hosmer-Lemeshow suggested good model fitting (chi square 7.07, df=8, *p*=0.528). The Receiver Operating Characteristics (ROC) Curve for the model had an AUC of 0.781.

Discussion

Comorbid diseases and non-supported discharge were significant predictors of repeated hospital admissions. Comorbidities was found to be associated with hospital readmissions in previous studies.[23, 24] The Charlson comorbidity index (CCI) is a commonly used measure of comorbidity in such studies, but involves a cumulative weighted scoring system to predict 10-year mortality risk. We did not utilise this as we endeavoured to use measures easily obtained whilst providing care by the bedside, i.e. simple cumulative number of comorbidities. The number of comorbid conditions may be an indication of a number of issues in this cohort of

patients. The existence of multiple comorbid conditions (i.e. multimorbidity) can have an impact on disease management burden, increased levels of care complexity, and increased risk of experiencing fragmented care[25, 26]. In addition, multimorbidity was found to be associated with decline in functional status and subsequent frailty[27]. With this in mind, while presence of comorbid conditions may be a significant predictor of RHAs, perhaps it is also an indicator of wider issues such as complexity, instability of disease management, fragmented care, and disease burden.

In previous studies, appropriate discharge support was shown to reduce RHAs. [28, 29] The intervention components included in these studies vary, making it difficult to assess the effectiveness of individual components. For example, is it post-discharge follow-up at home, or is it having re-ablement services[30] in place that makes a difference? It is also possible that those selected for supported discharge have been identified by extreme events and exacerbations, which might return to normal without active intervention.

Medicines-related risks were not found to be strongly associated with future RHAs in the multivariable logistic regression. Previous studies have found that polypharmacy, high risk medication, and diuretic use were associated with hospital readmission.[31-34] However, these studies did not take account of number of comorbidities, supported discharge and deprivation index in their multivariate logistic regressions.[31-34] This study is the first, to our knowledge, which looks comprehensively at a multitude of medication-related risk factors and their contributions towards repeated hospital admission in the elderly. It is also one of few studies looking at this topic within the NHS.

The number of comorbidities in this context may be driving repeated hospital admissions due to its complexity, instability, and management burden. Medicines-elated factors were significant only at univariate analysis, which it begs the question of the role of medicines in this cohort of patients with multimorbidity – is medicines beneficial, neutral or harmful? It is likely that hyper-polypharmacy adds to the complexity and burden of management; ‘when required’ medicines adds to the instability of medicines regimen; PIM and high risk medicines adds to all of the above. As the number of comorbidities in an individual is non-modifiable, one could argue that more support could be given at discharge to individuals with multimorbidity or medicines regimen simplified to reduce RHA risks. The role of deprescribing and medication review in frail elderly patients should be further explored. Emerging evidence endorses the safety and positive outcomes of simultaneous discontinuation of multiple medications in older people[35, 36]. Importantly, previous studies have shown that older people have the desire to reduce tablet burden, particularly if they take large number of medications, or if they are experiencing side effects.[37] In addition, closer monitoring of adverse effects of diuretics and other high risk medicines is important to ensure safe use of these

medicines. Lastly, enhancing the label instructions and patient education on the use of PRN medicines may help to reduce RHAs.

This study was the first study of its kind to examine multiple medication-related risk factors and their association with RHAs in a given timeframe. However, there were several limitations. Firstly, the integrity of the routinely collected data cannot be guaranteed. However, as this study uses data derived from electronic discharge summaries, clinical checking systems were in place to ensure the greatest accuracy possible. Secondly, the generalisability of our findings may be limited due to its conduct at a single hospital, although prevalence of medication-related risk factors was consistent with findings from other studies. Thirdly, participants' adherence to their medication prior to and after their hospitalisation was not assessed and any non-adherence could affect the observed associations between medication exposure and adverse outcomes. Lastly, even with inclusion of known confounders in our model, residual confounding, particularly due to medication indication, condition severity, and other unrecognised factors, may affect the observed associations between medication-related risk factors and RHAs.

Conclusion:

This is the first study to evaluate a combination of medication-related risk factors in predicting RHAs in the elderly. No association was found between medicines-related risks and RHAs in a multivariable logistic regression. However, the number of comorbidities and non-supported discharge was associated with RHAs. There may be scope to define the number of comorbid conditions needed to warrant supported discharge. In addition, interventions designed to reduce number of medicines and enhance safety of prescriptions e.g. deprescribing and increased monitoring; alongside increased patient education of management of PRN medicines could have a role in reducing repeated hospital admissions in the elderly. Further work is required to develop and evaluate risk prediction tools which incorporate medicines-related risks; along with targeted interventions to reduce medication-related RHAs.

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The dataset used to generate this manuscript will be used in the main author's PhD Thesis, which will be published on a public repository. It is anticipated that the dataset will not be used to generate further manuscripts.

AUTHOR DECLARATION/ AGREEMENT

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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