Research in Social and Administrative Pharmacy 19 (2023) 1048–1053

Contents lists available at ScienceDirect

Research in Social and Administrative Pharmacy

journal homepage: www.elsevier.com/locate/rsap

Exploring medication-related hospital admissions and their association with cognitive impairment among acutely admitted older people

Jonas Kindstedt [a,*], Pernilla Andersson [a], Annica Westberg [a], Eva-Lotta Glader [b], Hugo Lövheim [c], Maria Gustafsson [a]

[a] Department of Integrative Medical Biology, Umeå University, SE-901 87, Umeå, Sweden
[b] Department of Public Health and Clinical Medicine, Umeå University, SE-901 87, Umeå, Sweden
[c] Department of Community Medicine and Rehabilitation, Umeå University, SE-901 87, Umeå, Sweden

ARTICLE INFO

Keywords:
Cognitive impairment
Hospital admissions
Medication-related problems
Older people

ABSTRACT

Introduction: Medication-related hospital admissions (MRAs) are common among older people. Persons with cognitive impairment are especially vulnerable to adverse drug effects. At the same time, increased home health care and social support could theoretically prevent medication-related problems. This study aims to estimate the proportion of MRAs and explore their relationship with cognitive impairment in a population of acutely admitted older people.

Methods: This cross-sectional study comprised 300 individuals aged 75 years or older admitted to an acute medical ward. Two assessors identified possibly MRAs using the Assessment Tool for Hospital Admissions Related to Medications 10 (AT-HARM10). Screening for cognitive impairment was performed during ward stay using a 4-item test related to time orientation. Prevalence odds ratios between cognitive test scores and MRAs were analysed through logistic regression.

Results: Using AT-HARM10, 108 out of 300 admissions (36%) were classified as possibly MRAs by both assessors. Moreover, MRAs were least common among patients with the lowest cognitive test scores. There was an association regarding MRAs when the lowest test score was treated as a cut-off and compared against a reference category comprising all other scores (OR, 0.31 [95% CI 0.10–0.93]; p = 0.037) in a logistic regression model adjusted for cohabitation and home health care.

Conclusion: Approximately one-third of the hospital admissions among acutely admitted older people were considered at least possibly medication-related. Hence, there is still a great need to manage medication-related problems and reduce MRAs in this vulnerable population. Using a 4-item instrument to screen for cognitive impairment, there was a negative association between MRA and lowest cognitive test score. Further exploration of the relationship between MRAs and cognitive impairment may indicate appropriate components and target populations for interventions that aims to reduce the risk of MRA.

1. Introduction

Adverse drug reactions (ADRs) and other medication-related problems (MRPs) are likely to be involved in around 10–20% of unplanned hospitalizations among older people[1–3]; the figure may be even higher in the vulnerable subgroup of individuals with major neurocognitive disorder (NCD).[4] In that context, even milder forms of cognitive impairment can result in poor medication adherence[5] and might thus be detrimental for the long-term outcome in, for example, heart failure.[6–8] Therefore, even those with milder cognitive deficits that do not fulfil the criteria for major NCD but live independently (i.e., not in nursing homes or similar institutions) might be more likely to experience MRPs and associated hospitalizations. On the other hand, increased support in terms of home health care, dose dispensing or frequent home health care visits could potentially reduce susceptibility among these people to medication-related hospital admissions (MRAs).

The aim of this study was to estimate the occurrence of unplanned (i.e., non-elective) MRAs and explore their association with cognitive

* Corresponding author. Department of Integrative Medical Biology, Umeå University, Sweden, SE-901 87, Umeå, Sweden.
E-mail addresses: jonas.kindstedt@umu.se (J. Kindstedt), pernilla.andersson01@umu.se (P. Andersson), annica.westberg@regionvasterbotten.se (A. Westberg), eva-lotta.glader@umu.se (E.-L. Glader), hugo.lovheim@umu.se (H. Lövheim), maria.gustafsson@umu.se (M. Gustafsson).

https://doi.org/10.1016/j.sapharm.2023.04.117
Received 24 February 2023; Received in revised form 5 April 2023; Accepted 15 April 2023
Available online 16 April 2023

impairment in a population of acutely admitted older people. The first objective was to assess the proportion of MRAs in the study population as well as differences in odds of MRA depending on test results from a cognitive screening test. The second objective was to further analyse any significant associations adjusted for potential confounders and/or effect modifiers.

2. Method

2.1. Study population and sampling

This cross-sectional study included 300 individuals aged 75 years or older who had been continuously recruited at the acute medical ward at Umeå University Hospital from September 2018 to October 2021 for a clinical trial investigating the effect of clinical pharmacist intervention in transitions of care on medication-related hospital readmissions. The sampling and recruitment procedure are more thoroughly described in the published version of the study protocol,[9] but patients living in nursing homes were not eligible for the clinical trial, since the intervention was indented for people in ordinary homes, and were consequently not included in the present study. Similarly, people who during that period had declined to participate in the trial (n = 71) or withdrew their consent after enrolment (n = 19) were not included in the dataset. Due to the objectives and exploratory nature of the study, the sample size was not based on a power calculation. In brief, the whole sample (eTable 1) had a mean age of 84.2 years and included 188 (63%) females. Furthermore, 29 (10%) had a confirmed diagnosis of major NCD, of which 11 cases had been diagnosed with Alzheimer's disease, 10 with vascular dementia, 3 with Lewy body dementia and 5 with unspecified or other dementia. Medical support services in terms of dose dispensing and home health care had been initiated in 28% and 10% of the sample, respectively.

2.2. Assessments

The causality assessments of hospital admissions were performed using the Assessment Tool for Hospital Admissions Related to Medications 10 (AT-HARM10), a questionnaire originally developed by researchers at Uppsala University and validated in a population of older people.[10] All data for the study were gathered from electronic medical charts (NCS Cross) and included admission notes, medication list upon admission, laboratory values and epicrises. Before the study, the instrument itself was evaluated on 10 randomly selected hospital admissions of patients 65 years or older by three different pharmacists to identify and discuss potential issues regarding interpretations of the questions in specific types of patients and diagnoses. It was not considered realistic to set exact criteria for distinguishing between worsening condition and suboptimal treatment; however, it was determined that time from new or worsening symptoms until health care contact in combination with medication alterations during hospital stay were important circumstances to consider in those specific cases. Thereafter, 300 index-admissions from the intervention study were assessed through AT-HARM10 by two pharmacists (A1 and A2), of which one assessor (A1) also had completed a Master's Programme in Clinical Pharmacy. For administrative reasons, the other assessor (A2) was not blinded to the cognitive test scores.

The cognitive screening was carried out by staff during ward stay using a 4-item version of the Gottfries' cognitive scale.[11] In brief, these four items (number 16-19 from the original scale) related to time orientation and could result in scores from 0/4 to 4/4 positive/correct answers, with negative answers indicating cognitive impairment. A previous study by Lövheim et al.[12] showed a sensitivity and specificity of 97.8% and 92.5%, respectively, in relation to the full questionnaire, when allowing no more than one negative answer as a cut-off. When accepting a maximum of two negative answers, the sensitivity decreased to 93.8%, while the specificity increased to 98.6%.

As a sensitivity analysis, all possibly MRAs identified through AT-HARM10 by A1 and A2 were further assessed according to the WHO-UMC criteria for ADRs[13] by another clinical pharmacist (A3) who also had completed a Master's Programme in Clinical Pharmacy, in addition to accumulating eight years of experience working in the field. This assessor was blinded to the cognitive stratification and allowed to consult additional clinical pharmacists to reach a final judgement. For issues other than ADRs, for example, MRAs due to inadequate treatment (i.e., dosage too low, ineffective drug/inappropriate drug, need for additional drug therapy, non-adherence and interactions producing loss of therapeutic effect) that could exacerbate a patient's condition, assessments were conducted according to the same WHO-UMC criteria. In those cases, however, the following changes were applied: 'clinical event' was interpreted as 'exacerbation of symptoms', 'time relationship to administration of the drug' as 'time relationship between the start of inadequate treatment and the appearance of symptoms' and 'response to withdrawal of the drug' as 'response to adjustment to an adequate dosage'.

2.3. Statistics

The associations between 4-item Gottfries' test scores and MRAs (Table 1) were first analysed through simple logistic regression. In that analysis, test scores of 0/4–3/4 correct/positive answers were treated as dichotomous dummy variables using 4/4 positive answers as the reference category. The test score showing the strongest association with MRA was then tested as a cut-off against all other test scores combined in both simple and multiple logistic regression models. The latter analysis included cohabitation and home health care as covariates since these two factors were considered a potential confounder and effect modifier, respectively. Linearity between continuous variables and the logarithm of the odds was inspected graphically. Differences regarding descriptive data were analysed through either Pearson's Chi-Squared tests or One-Way ANOVA depending on the type of variable, and individuals with missing data were deleted pairwise. All tests were two-sided with a significance level of $p \leq 0.05$. IBM SPSS Statistics version 28 was used for all statistical analyses.

2.4. Ethical considerations

Informed consents were obtained from all study participants; however, in cases of confirmed major NCD, the next of kin was given the mandate to decline participation on behalf of their relatives. Personal data handling was performed within the framework of the concurrent clinical trial. The study was approved by the Swedish Ethical Review Authority (registration numbers 2020–05426, 2020–03699, 2017-69-31, 2018-254-32 and 2018-83-32).

3. Results

3.1. Proportions of MRAs

During the AT-HARM10 classification, the assessors A1 and A2 found 47% and 45% of the hospital admissions, respectively, to be possibly medication-related, with a percentage agreement of 79% and a 0.59 Cohen's kappa statistic (Fig. 1). In total, the two assessors agreed on 108 hospital admissions (36%) as possibly medication-related according to AT-HARM10, with an estimated population proportion of 0.31–0.42 (95% confidence level). Of the admissions that at least one assessor classified as unlikely MRA (n = 192), the agreement was 68%. The subsequent assessment using the WHO-UMC criteria resulted in 11 (10%) of the 108 hospital admissions being classified as unlikely MRAs, 74 (69%) as possibly MRAs and 23 (21%) as probably MRAs (Fig. 1). Another clinical pharmacist was consulted for a second opinion in 4 out of 108 WHO-UMC assessments.

Table 1
Sample characteristics according to cognitive test score.

Sample characteristics	4-item Gottfries' test score					P-value
	0/4 positive answers	1/4 positive answers	2/4 positive answers	3/4 positive answers	4/4 positive answers	
Number of individuals, n	27	31	43	89	110	n/a
Female sex, % (n)	59 (16)	68 (21)	58 (25)	62 (55)	65 (71)	0.903
Age,[a] mean ± SD	**84.5 ± 5.9**	**88.5 ± 5.9**	**83.2 ± 5.7**	**85.2 ± 5.9**	**82.4 ± 5.4**	**< 0.001**
Median age (IQR)	84 (8)	89 (10)	82 (10)	85 (9)	82 (8)	n/a
Major NCD, % (n)	**44 (12)**	**26 (8)**	**7 (3)**	**6 (5)**	**1 (1)**	**< 0.001**
Heart failure, % (n)	33 (9)	42 (13)	37 (16)	33 (29)	44 (48)	0.553
Cardiovascular disease,[b] % (n)	52 (14)	52 (16)	63 (27)	61 (54)	57 (63)	0.804
Hypertension, % (n)	67 (18)	71 (22)	72 (31)	72 (64)	72 (79)	0.988
Diabetes type 2, % (n)	33 (9)	29 (9)	28 (12)	23 (20)	31 (34)	0.697
Chronic obstructive pulmonary disorder, % (n)	7 (2)	7 (2)	14 (6)	8 (7)	19 (21)	0.100
Cancer (previous or current), % (n)	26 (7)	35 (11)	35 (15)	36 (32)	36 (40)	0893
Number of medicines,[c] mean ± SD	8.2 ± 3.3	8.2 ± 4.0	8.5 ± 4.2	7.9 ± 4.1	8.1 ± 4.0	0.936
Cohabitant, % (n)	**48 (13)**	**35 (11)**	**58 (25)**	**33 (29)**	**47 (52)**	**0.045**
Home care,[d] % (n)	**52 (14)**	**65 (20)**	**42 (18)**	**51 (44)**	**30 (33)**	**0.003**
Home health care, % (n)	**22 (6)**	**19 (6)**	**9 (4)**	**13 (12)**	3 **(3)**	**0.005**
Dose dispensing, % (n)	**52 (14)**	**61 (19)**	**35 (15)**	**28 (25)**	**11 (12)**	**< 0.001**

SD, standard deviation; IQR, interquartile range.
[a] Age refers to number of birthdays.
[b] Atrial fibrillation and/or myocardial infarction (present or previous) and/or stroke (previous or present).
[c] Treatments lasting >14 days with orally administered medicines or injections.
[d] Missing data for two individuals.

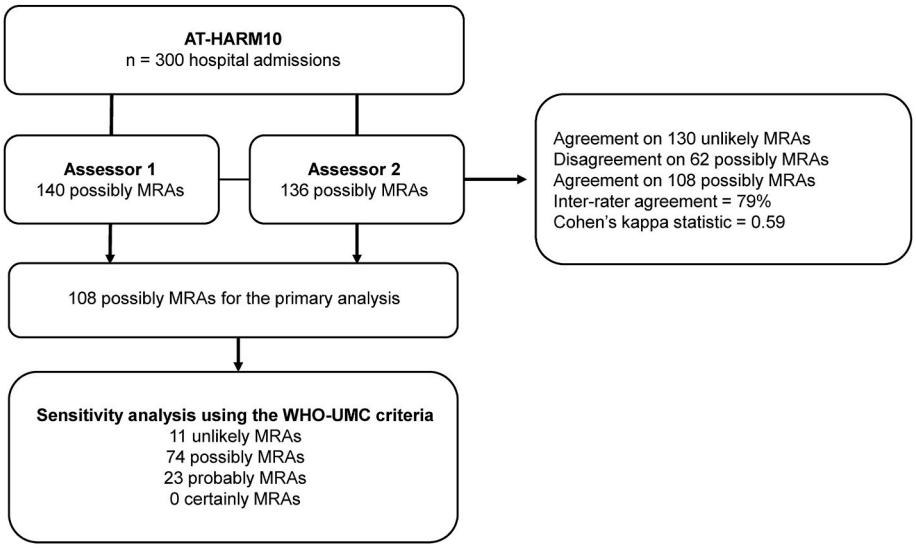

Fig. 1. Flowchart regarding assessment procedures, classification results and inter-rater agreement

3.2. Association between cognitive test score and MRAs

Regarding the 4-item Gottfries' test, more than a third of the patients (n = 110) scored positive on all four items. The distribution for the other test scores were: 3/4 positive answers, n = 89; 2/4 positive answers, n = 43; 1/4 positive answers, n = 31; and 0/4 positive answers, n = 27. The proportions of MRAs among patients with test scores 0–4 were 15%, 32%, 47%, 42% and 34%, respectively. Furthermore, among all patients with a confirmed major NCD diagnosis (n = 29), the corresponding proportion was 17%. Sample characteristics according to cognitive test scores are presented in Table 1. Overall, the groups were comparable in terms of all morbidities other than major NCD; however, patients with the lowest cognitive test scores were more reliant overall on social and medical support in terms of home health care, home care and dose dispensing. Using 4/4 positive answers as reference category, the odds ratio (OR) regarding test score and possibly MRA (Fig. 2) was lowest for those who scored negatively on all four items but not statistically significant (OR, 0.34 [95% CI 0.11–1.07]; p = 0.064). On the other hand, when treated as a cut-off (i.e., using all other test scores as reference category), there was a statistically significant association between lowest test score and MRAs (OR, 0.28 [95% CI 0.10–0.84]; p = 0.028). Lowest test score and confirmed diagnosis of major NCD did not show statistically significant associations with MRAs when included as covariates in the same regression model (eTable 2).

Adjusted for cohabitation and home health care, the association between test score and possibly MRAs was similar to the crude OR (Table 2). Among the other patient factors, major NCD and heart failure were both associated with possibly MRAs. Cohabitation was less common among patients with MRAs, but the difference was not statistically significant when analysed through simple logistic regression. Crude ORs regarding patient factors and MRAs are available in eTable3.

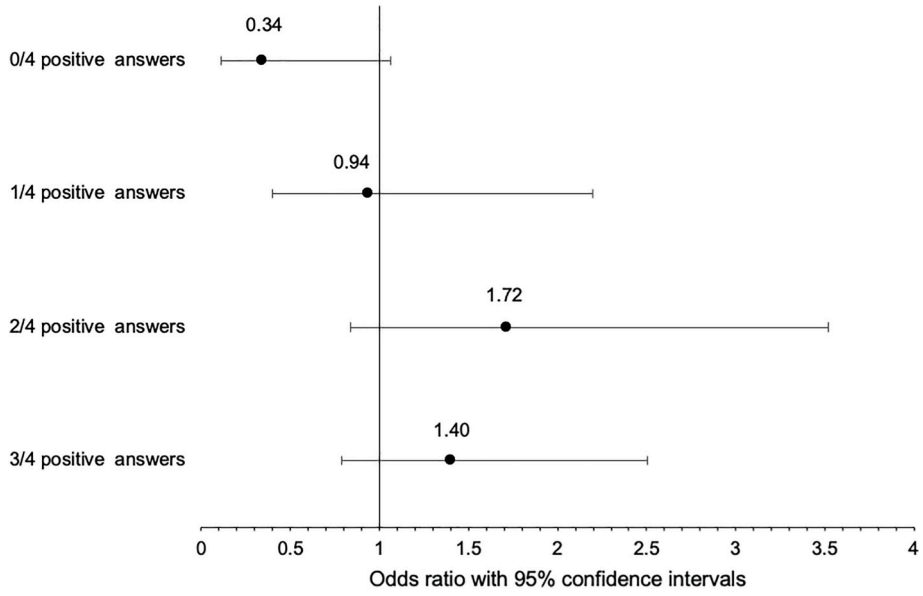

Fig. 2. Forest plot showing odds ratios regarding Gottfries' 4-item test scores and medication-related hospital admissions, using individuals with 4/4 positive answers as reference category

Table 2
Multiple logistic regression analyses regarding cognitive test score and medication-related hospital admission.

	Medication-related hospital admission[a]		
	OR	CI (95%)	P-value
Gottfries' 4-item test score[b]			
0 positive answers	0.31	0.10–0.93	0.037
Cohabitant	0.64	0.39–1.01	0.082
Home health care	0.48	0.19–1.19	0.111

Cox & Snell $R^2 = 0.050$; Hosmer and Lemeshow test 10.005, $p = 0.188$
CI, confidence interval; OR, odds ratio
[a] Classified as possibly medication-related, according to AT-HARM10
[b] Applying 1–4/4 positive answers as reference category.

3.3. Common MRPs

The most common types of MRP that both A1 and A2 identified among all possibly MRAs (n = 108) were ADRs (n = 22), followed by insufficient medication in terms of number of medicines (n = 21). An alternative way to summon and exemplify some of the most common MRPs is through the types of drugs and symptoms that both assessors agreed on as possible causes of admission. For instance, 28 hospital admissions were regarded as possibly related to cardiovascular causes (e.g., dizziness, syncope or orthostatic blood pressure), with beta-blocking agents being involved in 17 of those cases. Concerning heart failure, suboptimal treatment, poor adherence and/or failure to acknowledge any obvious symptoms of worsening condition over a period of several weeks were considered contributing factors in 16 admissions. Some other types of MRPs were: electrolyte imbalance (n = 7), primarily because of diuretics or selective serotonin inhibitors; infections due to drugs with immunosuppressive properties or medicines that otherwise could increase susceptibility to such diseases (n = 6); issues with glycaemic control (n = 5); and anaemia in patients using one or more drugs that increase bleeding risk (n = 5).

4. Discussion

4.1. Findings

In the present study, approximately one-third of the hospital admissions were classified as possibly medication-related, and there was a negative association between those specific hospitalizations and the lowest score on the 4-item Gottfries' test. Regarding the causality assessments of hospital admissions, it is difficult to compare the findings directly to previous reports due to differences in populations, settings and definitions of the term *medication-related*. No admission was classified as certainly medication-related according to the WHO-UMC criteria, which is an indicator that there is rarely one single factor involved. In that aspect, additional assessors with other medical backgrounds might have been able to rule out other causality and therby identify some admissions as certainly medication-related. When looking at the same age group (i.e., 75 years or older), a study of emergency department visits leading to hospitalization in the United States showed that almost half the annual rate of such events results from issues concerning therapeutic medication use.[14] On the contrary, a recent study from a similar Swedish health care setting of unplanned admissions addressed *reasonable* drug treatment[15] and found that in none of the 30 admissions was the intended drug regimen considered unreasonable. Given such shifting results depending on methods and definitions, it should be stressed that the intention of using AT-HARM10 was to capture as many types of MRAs as possible; the assessments are not limited to medication appropriateness and potential prescribing errors but also incorporate the perspectives and responsibilities of the patient, spanning from forgetfulness and misunderstandings to deliberate overuse of certain medicines. The observed percentage of MRAs was thus rather high compared to metadata showing that approximately one out of ten hospital admissions among people older than 60 years is due to ADRs[16] and highlights that, despite proper indication and adequate dosing, a reasonable drug treatment is no guarantee for an optimal patient outcome. Inadequate dosing or lack of additional medicines seem to be another issue for many older individuals, though it could be hard to distinguish between deteriorating condition and suboptimal treatment, especially among heart failure patients. For example, even if a heart failure treatment has been optimized in the first place, it is still crucial for the patient or caregiver to notice emerging or worsening dyspnoea or oedema[17] to prevent hospitalization; any failure to address such signs in a perspective of a few weeks was, according to our definition, generally considered a medication-related issue, except in cases of individuals with end-stage disease where the pharmacological treatment had already been fully optimized.

The Cohen's kappa statistic between the two different assessors was

0.59, which was in the range of the values (0.45–0.75) reported from the first validation of AT-HARM10.[10] However, in this type of study, the inter-rater agreement of 79% probably reveals more about the clinical utility of the classification tool.[18] Given that AT-HARM10 should primarily be used as an initial time-saving screening procedure to rule out MRAs that are highly unlikely, the most relevant statistic regarding AT-HARM10 may be the 68% agreement among the 192 admissions that at least one of the assessors classified as unlikely MRA.

The present study also explored the association between MRA and cognitive impairment through a combination of classification tools and found that patients with the lowest cognitive test scores had lower odds of MRA. Of note, even in that specific subgroup, less than half had a confirmed major NCD diagnosis, and our sample was thus notably different from an earlier MRA assessment among patients with major NCD conducted in the same setting.[4] The associations between the lowest cognitive test result and MRAs were consistent regardless of reference category; however, the result was only statistically significant when the test score was treated as a strict cut-off (i.e., comparing those with the lowest test score against the rest of the sample). In that aspect, it should be noted that using 4/4 positive answers as a reference category substantially decreased the number of individuals being compared from 300 to 137 and consequently resulted in a substantial loss of statistical power. Finally, the potential 0/4 positive answer cut-off was not statistically significant after adjusting for major NCD; hence, the results do not confirm whether the 4-item test can be of better clinical and scientific utility to distinguish between individuals with different odds of MRA than relying on a record of major NCD alone.

The results were not in line with the presumption that cognitive impairment may impede with medication use at a level that can be measured in terms of hospital admissions from a cross-sectional perspective. Although the statistical significance depended on reference group, the result might still have highlighted a group of patients rarely addressed in research contexts: individuals in independent households with previously unnoticed or undiagnosed forms of cognitive impairment but with relatively fewer clinically relevant MRPs than cognitively normal references. On the other hand, lower proportions of possibly MRAs among the cognitively impaired do not necessarily indicate that these persons have a lower risk of such events. Even though several comorbidities were less common among the cognitively impaired in the sample (Table 1), the results could nonetheless reflect competing risks from other causes of admission in that group (e.g., disease-related factors) resulting in relatively fewer MRAs over time. It is also likely that the adjusted OR could be confounded by other types of medical or social support that were not accounted for in the regression model. Many patients had a history of recent hospital visits; hence, most admissions assessed in this study could to some degree also be viewed as readmissions depending on time perspective, and in that context, the length and cause of previous hospital stays might be relevant.[2] Similarly, the differences in MRAs could be due to associated comorbidities rather than the level of cognitive impairment; for example, it is known that both cognitive impairment and MRAs are associated with heart failure.[19,20] The crude OR between heart failure and possibly MRAs was 0.55 and statistically significant (eTable3); however, uncertainties remain regarding missing diagnoses and disease severity, e.g., New York Heart Association (NYHA) classification. Such information was generally not available in the limited medical chart copies used for the assessments. Cohabitation has previously been associated with a lower risk of all-cause unplanned hospital admissions and/or emergency department visits among older people,[21,22] and the result regarding cohabitation and MRAs in the sample could reflect those findings, which indicates that the plausible protective factor might to some degree be related to a cohabitant managing the medicines.

Hospital admissions associated with suboptimal adherence have been estimated to comprise around 5% of all hospitalizations involving older people.[23] During the assessment procedure, sufficient adherence was assumed by the assessors if no such issues were directly or indirectly suggested in physicians' notes. Dispensing data and/or patient interviews could have contributed to a more complete picture regarding drug use prior to hospitalization and consequently a higher proportion of MRAs.

Taken together, it seems more likely to find MRAs in populations with less pronounced cognitive deficits, which could be relevant knowledge in the management of medication-related issues. Depending on cognitive impairment, some older people may be more suitable targets than others for pharmaceutical interventions that aim to reduce MRAs and similar clinical outcomes, but the relationships need to be better investigated in terms of risk, for example, through a cohort study using a similar setting and study population. From a clinical or patient perspective, however, the exact label of a hospital admission is perhaps not relevant if there are available means for reducing them. The association between cognitive impairment and all-cause admissions is also highly relevant but could not be explored within the frameworks of this study, since the dataset was based exclusively on hospital admissions to begin with.

4.2. Strengths

Since every case included in the final analysis had been confirmed as possibly MRA by two different assessors, the risk of overestimation and misclassification was minimized. Another strength is the relatively broad eligibility criteria which ensured that few individuals were directly excluded based on specific diagnoses. The study population should therefore, with the exception of nursing home residents, be representative of older people encountered in emergency care settings.

4.3. Limitations and risk of bias

The main limitation of this study was the methodological complexity in classifying medication-related events, and including additional assessors with different medical background would have improved validity. It should be stressed, however, that physicians' notes from the clinical ward were used by the assessors; hence, some valuable input from other medical professions indirectly guided the classifications. This study incorporated two classification tools as well as a cognitive screening test, and some of their psychometric properties deserve to be mentioned. For example, the test–retest reliability of the 4-item Gottfries' test is one potential source of bias since acutely admitted patients might have been classified as cognitively impaired due to temporary states of confusion, either as the primary cause of admission or emerging during hospital stay.[24] Delirium could also be seen as a potential confounder that might have affected the observed association in either direction. However, delirium was not included as a covariate in the regression analysis, since it was regarded as a potential collision factor that could bias the results.[25] It should also be noted that cognitive impairment is the leading risk factor for delirium,[26,27] and cases of lower test scores due to delirium could nonetheless be an important indicator of underlying cognitive deficits. Finally, it should also be highlighted that the 4-item Gottfries' test has not been validated as a measure regarding severity of cognitive impairment; however, that was not in conflict with the study objectives. Taken together, the 4-item Gottfries' test could have, despite some uncertainties, distinguished relevant comparison groups in terms of cognitive impairment and MRAs, even if it did not necessarily correspond to other measurement scales for cognitive impairment or major NCD (e.g., Mini Mental State Examination).[28] Concerning the causality assessments of the hospital admissions, they were all based on the same limited patient information, and the WHO-UMC criteria were probably not utilized with full capacity to validate the AT-HARM10 classifications. The proportions of possibly MRAs according to the WHO-UMC criteria might have been slightly overestimated, and some admissions might have fallen into categories of either higher or lower probability if the assessor had been given full electronic access to medical records. Another potential limitation

concerning the assessments of MRAs was that, due to concurrent involvement in the concurrent clinical trial,[9] the secondary AT-HARM10 assessor (A2) was not blinded with respect to the Gottfries' 4-item test scores. In addition, even without information regarding the cognitive screening, signs of cognitive impairment were sometimes implied in the medical records, which could have disrupted the blinding of test scores. That, however, should not have been a major issue in the assessments, since the approach of the study was foremost exploratory rather than confirmatory.

5. Conclusions

Approximately one-third of the hospital admissions among acutely admitted older people were considered at least possibly medication-related. Hence, there is still a great need to manage MRPs and reduce MRAs in this vulnerable population. Using a 4-item instrument to screen for cognitive impairment, the results showed a negative association between MRA and lowest cognitive test score. Further exploration of the relationship between MRAs and cognitive impairment in terms of underlying mechanisms, incidence and relative risk may indicate the most appropriate components and target populations for future interventions that aims to reduce the risk of MRA.

Ethical approvals

The Swedish Ethical Review Authority approved this study (registration numbers 2020–05426, 2020–03699, 2018-254-32, 2018-83-32 and 2017-69-31).

Availability of data and material

The datasets generated during and/or analysed in the present study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Authors' contributions

JK wrote this manuscript and ran the statistical analysis. JK and MG developed the principal study design. AW (A1) and JK (A2) performed the AT-HARM10 assessments. PA (A3) did the WHO-UMC assessments and provided valuable input regarding the study design and assessment tools. JK, AW, PA, ELG, HL and MG contributed to the revision of the study protocol and were involved in the review process of the manuscript. All authors approved the final version and will ensure that issues related to the accuracy or integrity of the work are investigated and resolved.

Funding

This study is supported financially by grants from Region Västerbotten, Umeå University Foundation for Medical Research, Forte (ref: 2017–01438) and the Swedish Research Council (ref: 2019–01078). The funders have no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2023.04.117.

References

1. Chan M, Nicklason F, Vial JH. Adverse drug events as a cause of hospital admission in the elderly. *Intern Med J*. 2001;31(4):199–205.
2. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and preventability of drug-related hospital readmissions: a systematic review. *J Am Geriatr Soc*. 2018;66(3):602–608.
3. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014 Dec 1;9:2079-86.
4. Gustafsson M, Sjolander M, Pfister B, Jonsson J, Schneede J, Lovheim H. Drug-related hospital admissions among old people with dementia. *Eur J Clin Pharmacol*. 2016;72(9):1143–1153.
5. Hayes TL, Larimer N, Adami A, Kaye JA. Medication adherence in healthy elders: small cognitive changes make a big difference. *J Aging Health*. 2009;21(4):567–580.
6. Tang HY, Sayers SL, Weissinger G, Riegel B. The role of depression in medication adherence among heart failure patients. *Clin Nurs Res*. 2014;23(3):231–244.
7. Ruppar TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5(6).
8. Wise J. Cochrane review says telephone follow-up of heart failure patients is effective. *Bmj*. 2012;345:e6187.
9. Kindstedt J, Svahn S, Sjölander M, Glader EL, Lövheim H, Gustafsson M. Investigating the effect of clinical pharmacist intervention in transitions of care on drug-related hospital readmissions among the elderly: study protocol for a randomised controlled trial. *BMJ Open*. 2020;10(4), e036650.
10. Kempen TGH, Hedstrom M, Olsson H, et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. *Int J Clin Pharm*. 2019;41(1):198–206.
11. Gottfries CG, Gottfries I, Roos BE. The investigation of homovanillic acid in the human brain and its correlation to senile dementia. *Br J Psychiatry*. 1969 May;115(522):563–574.
12. Lovheim H, Gustafsson M, Isaksson U, Karlsson S, Sandman PO. Gottfries' cognitive scale for staff proxy rating of cognitive function among nursing home residents. *J Alzheimers Dis*. 2019;72(4):1251–1260.
13. Uppsala Monitoring Centre. *The Use of the WHO-UMC System for Case Causality Assessment: Uppsala Monitoring Centre*; 2018. Available from https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf.
14. Budnitz DS, Shehab N, Lovegrove MC, Geller AI, Lind JN, Pollock DA. US emergency department visits attributed to medication harms, 2017-2019. *JAMA*. 2021;326(13):1299–1309.
15. Lönnbro J, Holmqvist L, Persson E, Thysell P, Åberg ND, Wallerstedt SM. Inter-rater reliability of assessments regarding the quality of drug treatment, and drug-related hospital admissions. *Br J Clin Pharmacol*. 2021;87(10):3825–3834.
16. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol*. 2017;73(6):759–770.
17. Takei M, Harada K, Shiraishi Y, et al. Delay in seeking treatment before emergent heart failure readmission and its association with clinical phenotype. *J Intensive Care*. 2020;8:65.
18. de Vet HC, Mokkink LB, Terwee CB, Hoekstra OS, Knol DL. Clinicians are right not to like Cohen's κ. *Bmj*. 2013;346:f2125.
19. Donzé J, Lipsitz S, Bates DW, Schnipper JL. Causes and patterns of readmissions in patients with common comorbidities: retrospective cohort study. *Bmj*. 2013;347:f7171.
20. Klinge M, Aasbrenn M, Öztürk B, et al. Readmission of older acutely admitted medical patients after short-term admissions in Denmark: a nationwide cohort study. *BMC Geriatr*. 2020;20(1):203.
21. Pimouguet C, Rizzuto D, Lagergren M, Fratiglioni L, Xu W. Living alone and unplanned hospitalizations among older adults: a population-based longitudinal study. *Eur J Publ Health*. 2017;27(2):251–256.
22. Hastings SN, George LK, Fillenbaum GG, Park RS, Burchett BM, Schmader KE. Does lack of social support lead to more ED visits for older adults? *Am J Emerg Med*. 2008;26(4):454–461.
23. Mongkhon P, Ashcroft DM, Scholfield CN, Kongkaew C. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. *BMJ Qual Saf*. 2018;27(11):902–914.
24. Barron EA, Holmes J. Delirium within the emergency care setting, occurrence and detection: a systematic review. *Emerg Med J*. 2013;30(4):263–268.
25. Holmberg MJ, Andersen LW. Collider Bias. Jama. 2022;327(13):1282-3.
26. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911–922.
27. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. *Lancet Neurol*. 2015;14(8):823–832.
28. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev*. 2016;(1):Cd011145.