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Types, predictors, and consequences of medicines related problems (MRPs) in frail older adults admitted to hospital from primary care - A retrospective cohort study

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ABSTRACT

Introduction: Medicines related problems (MRPs) can be common in frail older people due to age-compromised body systems and a propensity to be on multiple drugs concurrently. This group of people can also succumb to a rapid deterioration in health. Thus, it is important to investigate MRPs in frail older people. The objectives of the study were to evaluate prevalence of MRPs, types of MRPs, risk factors and deterioration that can be associated with MRPs in frail older people admitted to an English teaching hospital from primary care.

Methods: Included in the sample were frail older adults, aged 65 years and over, admitted from primary care. Data was retrieved from the hospital's electronic patient record system, anonymised, and reviewed for MRPs. MRPs which were retrospectively identified at admission were coded with the WHO-ICD10,2016 (World Health Organisation-International Classification of Diseases version 10, 2016). Descriptive and inferential statistics were performed on the data using SPSS Version 25. Primary outcome was the prevalence of MRPs in frail older patients. Secondary outcome was the association of deterioration indicated as fall, delirium, or NEWs $\geq$3 with presence of MRPs.

Results: Among the 507 frail older people ($\geq$4 on Rockwood scale) that met criteria for inclusion, 262 (51.8%) were patients with MRPs and 244 (48.2%) without. The Median age of sample as a whole was 85 years (*IQR = 80–89)*. Prevalence of MRPs was 33.28%. Types of MRPs were adverse drug reaction (ADR-20%), non-compliance (9.1%), unintentional poisoning (3.3%) and inappropriate polypharmacy (0.8%). In logistic regression, potentially inappropriate medicines (PIM), social support, number of comorbidities and winter were significant predictors of MRPs. Risk of deteriorating with delirium was two times higher in patients with MRPs than in patients without MRPs, RR 2.613 (95% CI, 1.049 to 6.510).

Conclusion: MRPs and risks of deterioration associated with MRPs in frail older people can be reduced. This is because factors associated with MRPs can be modified.

1. Introduction

Safe use of medicines in older adults can be challenging. This is because physiological changes that occur with ageing can interfere with an older person's ability to metabolise and excrete medicines. The result of this interference is increased sensitivity and reduced tolerance to several classes of medicines.[1] These effects potentially increase risk of medicines related problems (MRPs). An MRP or DRP (drug related problem) is defined as "an event or circumstance involving drug treatment that actually or potentially interferes with optimal outcome from medical care.[2]" This situation can be made worse by inappropriate polypharmacy which is the concurrent use of multiple drugs by one person with a reduced chance of clinical benefits and an increased risk of harm.[3] Inappropriate polypharmacy and its's associated risks are common features in older peoples' medication use[3] and more so in frail older adults.

Frailty is a state of increased clinical vulnerability as a result of predominantly age or disease related compromise in several

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physiological systems of a person.[4,5] Frailty defined as aged >65 years and needing ongoing hospital care from chronic disabling conditions, has been associated with impaired metabolism of certain medicines[6]. This highlights the importance of frailty in the health of older adults and in their bodies' medication handling. It underscores the importance of carrying out investigations to identify MRPs in frail older adults, notably those from primary care as most events that present in hospitals originate in primary care.[7]

Identification of MRPs can be achieved through structured medication review. Two broad approaches referred to as explicit and implicit[8,9] approaches respectively can facilitate the process of MRPs identification. The implicit approach involves a clinician applying expert knowledge to make medicines related assessments. Examples of implicit tools that have been applied to aid identification of MRPs are the medication appropriateness index (MAI)[10] and the Garfinkel algorithm.[11] The explicit approach is based on the use of expert consensus validated criteria to assist the process of MRPs identification within medication review. Examples of explicit tools that can assist identification of MRPs are the STOPP-START criteria,[12] the PRISCUS List,[13] the STOPP-Frail criteria,[14] the WHO-UMC causality tool,[15] the WHO-IC10 system (World Health Organisation international classification of diseases version10). STOPP-START, PRISCUS list, and STOPP-Frail tools can be considered as facilitators in the identification of MRPs since they are designed to identify potentially inappropriate medicines (PIMs) and PIMs can cause MRPs.[2]

A number of MRPs were suggested by Hepler and Strand in their 1990 seminal paper,[2] including untreated indication, subtherapeutic dosage, failure to receive a drug, overdosage, drug use without indication, adverse drug reaction (ADR)[2] and medication error.[2,16,17] Other studies cited relationship between frailty, MRPs[5,18–20] and adverse health outcomes.[21–23] However, there is limited knowledge in the literature focused on MRPs in frail older people from primary care. Unlike other published studies this study is an empirical study investigating concurrently, a number of MRPs and a number of indicators of deterioration potentially prevalent in frail older adults from primary care including own homes and care homes. The indicators of deterioration for this study are delirium, fall, hospitalisation and NEWS ≥3 (National early warning score ≥ 3).

Hence, the aim of the study was to investigate medicines related problems in frail older adults from primary care. The objectives of the study were to evaluate prevalence of MRPs, types of MRPs, risk factors and consequences such as deterioration that can be associated with MRPs in frail older adults admitted to an English teaching hospital from primary care.

2. Methods

2.1. Design and setting

This was a retrospective cohort study guided by the statement for 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)'. The number of patients presenting with each type of MRPs in the cohort was identified. The occurrence of falls, delirium, National Early Warning Score (NEWS) ≥3 and the deterioration score were investigated and compared between frail older adults with MRPs and those without. Patients' demographics, exposure, and outcome variables over an 18-month period from January 2017 to June 2018 were collected retrospectively from an anonymised patients' electronic hospital records. The study was set in a tertiary hospital in the East of England, a referral centre that provided full range of clinical services.

2.2. Sample and process of data collection

The population of interest was frail older adults, who were 65 years and older and admitted through Accident and Emergency (A&E) from primary care.

A sample size and power calculation for exposed and non-exposed on STATCALC module for Epi info version 7 from CDC Atlanta for epidemiology was employed. A confidence interval of 95% and power of 90% (alpha = 0.05 and 1-beta = 0.90) were assumed and a sample size of 600 calculated.

On presentation, doctors would routinely record patients' presenting complaints and reasons for admission. These complaints and reasons for admission were coded retrospectively by trained coders from the Coding department in the hospital. They were not part of the research team. The coding was achieved by applying the WHO ICD10 (World Health Organisation International Statistical Classification of Diseases and related health problems,10th revision). The codes that were relevant to this study included: T36-T50 (poisoning by drugs, medicaments and biological substances, +/− X40-X44 to indicate if these were accidental or unintentional poisoning and toxicity; Z91.1 (non-compliance with medicine); Y40-Y59 (drugs, medicaments and biological substances causing adverse effects in therapeutic use); ICD-10 UK Z51.8 (polypharmacy).

At the request of the research team, a report on medication related emergency admissions was generated by the hospital Informatics team. They were not part of the research team. The reports included patients with frailty scores who had been assessed for frailty with the Rockwood scale by A&E doctors within 24 h of admission, aged 65 years and over, non-electively admitted, with one or more of WHO ICD10 MRPs codes (World Health Organisation International Statistical Classification of Diseases and related health problems,10th revision) associated with an encounter. A second report was generated of patients with encounters not associated with the WHO ICD 10 MRPs codes.

Patients with MRPs were identified with the MRPs linked WHO ICD10 code, and a comparator group, without MRPs had no MRPs linked ICD10 codes. This report generated an electronic pool of patients as a sampling frame. The sample was randomly selected from this electronic pool of patients. Patients admitted electively and patients admitted for planned chemotherapy were excluded. Second and subsequent emergency admissions were excluded for patients who had multiple emergency admissions between January 2017 and June 2018. Thus, only the first admission for any given patient was included this was to make data uniform and manageable within time for the study. Within each group, data was sorted by admission date from the oldest to the newest and the first 16 and 17 patients admitted were alternately selected from individual months between January 2017 and June 2018 (Fig. 1). Demographics, frailty score, presenting complaints, National Early Warning Score (NEWS), comorbidities, MRPs, medicines, dates admitted, dates discharged and laboratory results which were recorded within 24 h of patient's admission, were all collected into an internally validated form. The British National Formulary (BNF), the Electronic Medicine Compendium (EMC), WHO ICD10, 2016, the Lab Tests Online as well as clinical knowledge were employed in interpreting data.

2.3. Variables

Frail older adults were adults aged 65 years and over who scored 4 or above on the Rockwood frailty scale within 24 h of admission. Deterioration in health was to get worse or decline in health[24]and was indicated with fall, delirium, NEWS ≥3, and hospitalisation. The degree of deterioration was quantified with a deterioration score. A deterioration score was made up of the total number of indicators present in a case (patient). The scoring method was agreed on by the chief investigator (NU) and a principal investigator (RO). It was validated through the expert panel's consensus.

MRPs were adverse drug reaction (ADR), non-compliance with medicines, poisoning/toxicity, and inappropriate polypharmacy. Reasons for admission were clerked by the doctors and coded by trained coders. The codes which indicate that hospital admissions were linked to MRPs[25] were identified independently by three principal investigators (RO, RB &EB) who were all clinical pharmacists and two of whom were

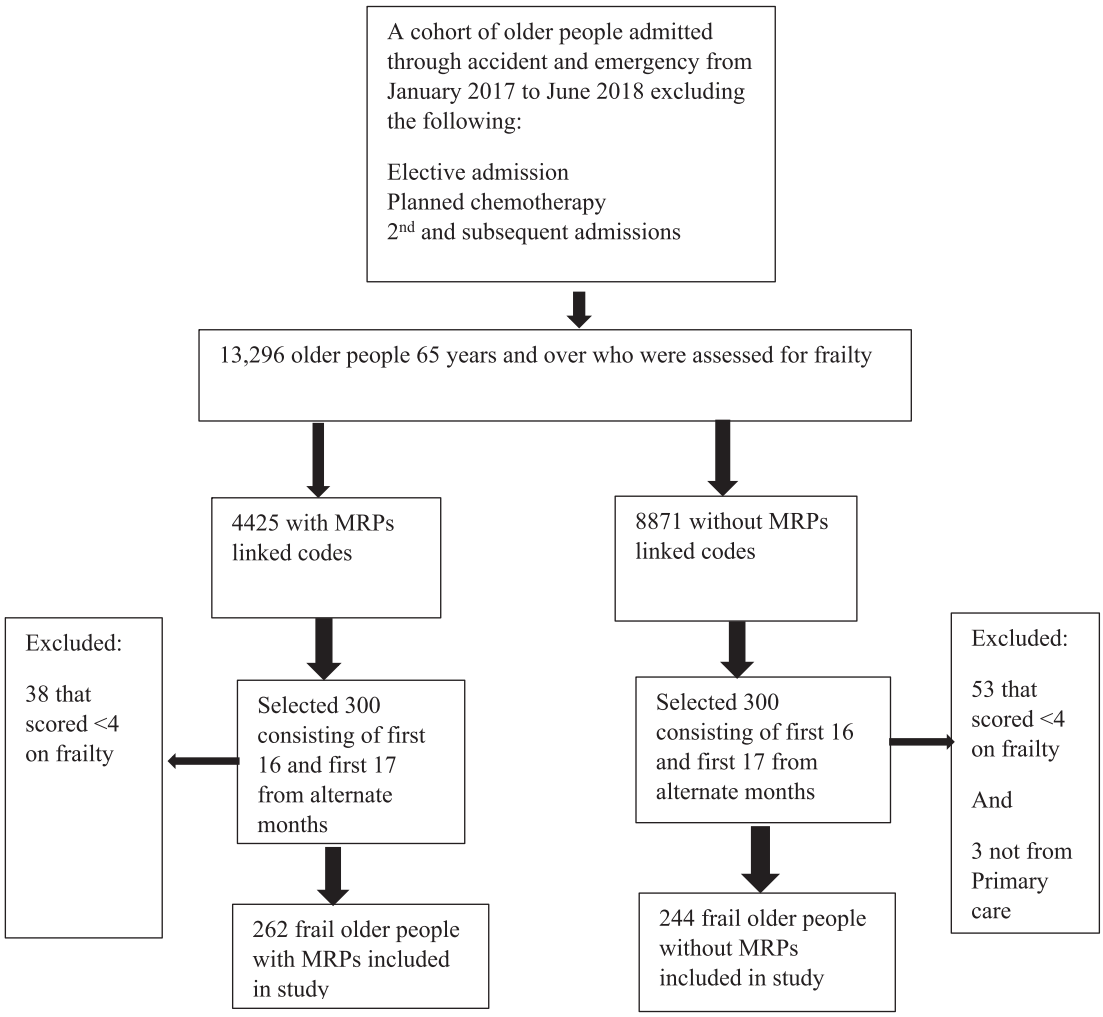

Fig. 1. Participants selection process diagram.

lead pharmacists in frailty and older people care at the time of the study. Any disagreements among the principal investigators about an MRPs were discussed and resolved over the telephone.

A fall was an event that resulted in a person coming to rest inadvertently on the ground or floor or other lower level. Within the WHO database fall-related deaths and non-fatal injuries exclude those due to assault and intentional self-harm. Falls from animals, burning buildings and transport vehicles, and falls into fire, water and machinery were also excluded.[26] Collapse was included as fall.

Delirium was defined as a sudden state of mental confusion and hospitalisation was staying for twenty-four or more hours in hospital and receiving a form of medical care.

NEWS is based on 6 physiological parameters that are normally measured in hospital which are: Pulse rate, blood pressure, respiratory rate, oxygen levels, temperature, and conscious level. The variations of these parameters from normal in ill patients are scored. A score of 3 in any one parameter or an aggregate score of 5 or more is an indication for triaging for response in patients.[27]

2.4. Data analysis

An adapted WHO-UMC causality tool was employed as a decision algorithm for causality of MRPs for deterioration. The tool was reviewed and validated through reimbursable work of an expert panel. Members of the expert panel were purposively recruited for their interest in patient safety research of older people. The panel comprised of clinicians including, a senior registrar in geriatric medicine, a hospital-based specialist pharmacist in older people care and a senior primary care pharmacist. Their level of agreement was determined by Cohen's Kappa (K).

Further analysis of data was undertaken descriptively and inferentially, using SPSS version 25.

In order to calculate prevalence of MRPs in frail older adults, the numerator was number of frail older adults with MRPs on admission and denominator was total number of frail older adults admitted.

A Kolmogorov-Smirnov test for normality was carried out for different variables as appropriate. Bivariate analysis including Mann-Whitney *U* test, and Chi-square test of homogeneity (2 X C) was used to determine differences between groups in continuous/ ordinal and categorical variables, respectively. Similarly, Chi-square test of independence (RXC table), Chi-square test for association (2 × 2 table) and relative risk (RR) were applied to understand relationships between MRPs and deterioration. Relative risk (RR) was calculated as the measure of association to show any differences in risk between the group with MRPs and the group without MRPs. Binomial logistic regression was applied to investigate variables that can predict MRPs. These potentially confounding variables which were season/time of year of visit, gender, age, ethnicity, residence, frailty, number of medicines, presence of potentially inappropriate medicines (PIM), number of comorbidities, and social support were first investigated as differences in group with MRPs and that without, through bivariate analysis. This was then followed by binomial logistic regression. The ten variables

were fed into a binomial logistic regression model. Linearity of continuous variables in the model with respect to the logit of MRPs was assessed via the Box-Tidwell 1962[28] procedures. All statistical tests were set at level of significance of 0.05.

2.4.1. Determination of prevalence of MRPs in frail older people

Estimation of prevalence using emergency admission of frail older adults with MRPs from 1st of January 2017 to 30th of June 2018 as the numerator and the total number of emergency admissions of frail older people in the same period as the denominator.

2.4.2. Investigation of reliability of assessors and validity of the measuring instrument for the assessment of deterioration, causality, degree of harm and preventability of harm

A random fraction of cases was presented as vignettes to three independent assessors for assessment. The cases assessed were exactly the same for each independent assessor. Response to each category was dichotomised to assess validity. Cohen's Kappa was applied as a statistical test for level of agreement between the assessors.

2.4.3. Distribution of frailty, NEWS, falls and delirium in group of patients with MRPs and those without MRPs

Descriptive analysis was undertaken to determine median and interquartile range of NEWS and frailty, then comparison was drawn between group with MRPs and that without.

The frequency of falls and delirium was calculated and compared between groups of MRPs and non-MRPs to identify any differences between groups. Mann-Whitney *U* test, Chi-square test of homogeneity (2 X C) were the statistical tests applied.

2.4.4. Identification of MRPs and implicated medicines. Estimation of proportion of patients in each category of MRPs

One principal investigator (RO) linked MRPs linked WHO ICD 10 linked codes to the class of medicines implicated in MRPs. The implicated medicine was then identified from the patients list of medicines. This was achieved with the help of the BNF, and the EMC. The proportion of each MRP was calculated using the frequency function on SPSS and MRPs were linked to the implicated medicines using the cross-tabulation tool.

2.4.5. Identification and classification of reasons for medicines related emergency admissions. Estimation of proportion of patients in defined categories

The reasons for medicines related emergency admissions were identified from the report on medication related emergency admissions generated by the Informatics team. The proportions of patients affected were calculated using the frequency function in SPSS.

2.4.6. Identification of factors that were associated with MRPs

Chi-square test of independence (R X C); Chi-square test for association (2 × 2); Relative Risk (RR); Binomial Logistic Regression.

2.4.7. Identification of potentially inappropriate medicines (PIM)

The STOPP (Screening Tool of Older Person's Prescription) 2008 was used to ascertain presence of potentially inappropriate medicines (PIM) in the cohort.

2.5. Ethical approvals

Ethical approval was given by the University of Hertfordshire Ethics Committee (LMS/PGR/NHS/02907) (UH REC) and the Health Research Authority (18/WM/0303).

3. Results

A diagrammatic presentation of participants' selection process is presented here (Fig. 1).

The results of the Kolmogorov-Smirnov tests for normality of age of participants, length of hospital stay, number of medicines, and number of comorbidities, showed non-normal distributions.

3.1. Prevalence of MRPs in frail older people

Prevalence of MRPs in frail older adults admitted from Primary care was 33.28%. Of the patients admitted with MRPs, 158 (20%) were due to ADR, 72 (9.1%) were due to non-compliance, 26 (3.3%) were due to unintentional poisoning, and 6 (0.8%) were due to inappropriate polypharmacy.

3.2. Reliability, validity of instrument and agreement between independent assessors

Agreement on causality of MRPs for reasons of admission was poor ($K < 1$) among the three experts who applied the adapted tool in analysing a subset of the data. An agreement for MRPs as possible cause of deterioration was in an average of 42.9% of the cases (one expert identified MRPs as possible cause of deterioration in 28.8% of the cases, another in 44.4% of the cases and a third, in 55.5% of the cases).

3.3. Summary of factors associated with MRPs

In bivariate analysis the significant differences in characteristics between the group of frail older people that had MRPs and those that had no MRPs were (Table 1), the presence of STOPP potentially inappropriate medicines (PIM), the residential status, the absence of social support, being a white British, the number of medicines that a patient was on and the number of comorbidities that a patient had, However, significant predictors of MRPs indicated by multivariate analysis were, the presence of STOPP-START PIM, absence of social support and the number of comorbidities.

3.4. Reasons for medicines related emergency admission

The top 5 reasons for emergency hospital admission due to MRPs were fall 72 (29.0%), shortness of breath 20 (8.3%), delirium 17 (7.0%), malaise 11 (4.6%) and abdominal pain 10 (4.2%). Patients with pre-existing hypertension and diabetes either alone or in combination were more likely than those without these conditions, to have falls and/or develop delirium from MRPs.

3.5. Medicines implicated in MRPs

The medicines commonly implicated in MRPs were medicines for the cardiovascular system (CVS) affecting 184 (70.2%); the central nervous system (CNS) affecting 93 (35.5%); the endocrine system affecting 52 (19.5%). The top four medicines for cardiovascular diseases were furosemide, bisoprolol, indapamide and lercanidipine. The top four medicines for the CNS were codeine, buprenorphine, citalopram and meptazinol. The top four medicines for endocrine were prednisolone, insulin aspart, metformin and insulin glargine. Furosemide was the medicine most implicated in MRPs, occurring 34 times in 262 cases.

Table 1 presents differences in characteristics between the two groups (with and without MRPS). There were significant differences in, ethnicity, residence, number of medicines, presence of PIM (potentially inappropriate medicines), number of comorbidities and social support between those with MRPs and those without. Differences in gender (female or male), age and frailty between the two groups, were non-significant.

Result of logistic regression analysis (Table 2) showed significant ($P \leq .05$) predictors of MRPs to be, the presence of PIM, having no social support, and the number of comorbidities.

Table 1
Characteristics of frail older people admitted on emergency from Primary care.

Variable	Whole sample: N: 597 Age: (median; IQR) Frailty:(median, IQR)	MRPs group n (%) 300 (50.3%) (262 frailty ≥ 4)	Non-MRPs group n (%) 297 (49.7%) (244 frailty ≥ 4)	Chi-Square	Mann Whitney *U* test value	*P*-value
Season of visit to A&E: n (%)						
Winter: (Dec-Feb)						
Spring: (March–May)	181	91 (50)	90 (50)	8.367	NA	0.039
Summer: (June–August)	191	96 (50)	95 (50)			
Autumn: (Sept-Nov)	137	69 (50)	68(50)			
	88	44 (50)	44 (50)			
Gender: n (%)						
Female	345	172 (50)	173 (50)	0.177	NA	0.679
Male	250	129 (52)	121 (48)			
Age:						
Median	85	85	85	NA	42,713	0.938
IQR	80–89	80–89	80–90			
Ethnicity						
n (%)						
White British	475	241 (51)	234 (49)	7.399	NA	0.007
Other	24	19 (79)	5 (21)			
Residence						
n (%)						
Care home	59	20 (34)	39 (66)	7.152	NA	0.007
Own home	536	280 (52)	256 (48)			
Frailty						
Median (med)	5.0	6	5.0		43,283.0	0.821
(IQR)	4–6	5–6	4–6			
No of medicines per patient						
Median	10	11	10	NA	38,649.5	0.004
IQR	7–14	7–14	7–13			
Potentially inappropriate medicines (PIM) n (%)						
PIM absent	435	191 (44)	244 (56)	25.896		<0.001
PIM present	150	102 (68)	48 (32)			
Number of comorbidities						
Median	6	7	5	NA	37,698	0.020
IQR	3–9	4–11	3–8			
Social support n (%)						
Has social support.	303	134 (44)	169 (56)	15.556		<0.001
Has no social support	180	113 (63)	67 (37)			

Table 2
Predictors of MRPs.

Variable	Odds Ratio	95% CI	P-value
Presence of PIM	0.392	0.235–0.653	**<0.001**
Having no social support	2.142	1.346–3.406	**0.001**
Number of comorbidities	1.089	1.030–1.152	**0.003**
Time of year			
Winter	2.513	1.267–4.9840	**0.008**0
Spring	1.401	.726–2.7040	.3150
Summer	1.127	.557–2.281	.739
Being a White British	2.845	0.921–8.789	0.069
Number of medicines	1.036	0.989–1.084	0.135
Age on admission	0.974	0.938–1.012	0.181
Living in own home	1.535	0.713–3.304	0.273
Gender	0.851	0.551–1.313	0.465
Frailty	1.038	0.886–1.217	0.642

3.6. Factors that predict MRPs in frail older people (Table 2)

Based on the result of the Box-Tidwell 1962[28] assessments, all continuous independent variables were found to be linearly related to the logit of MRPs. Furthermore, result of the Hosmer and Lemeshow test was not statistically significant ($P = .253$) indicating that the Binomial logistic regression model was not a poor fit. The model correctly predicted 62.1% of cases to have MRPs and was statistically significant, χ^2 (9) =53.125, $P < .0005$. Three of the ten predictor variables fed into the model were found to be statistically significant. These were, presence of PIM, absence of social support and number of comorbidities, (Table 2). Participants with no social support defined as single and living in own home were twice more likely to be exposed to MRPs than those with social support defined as living with a partner or living in a care facility. The result shows a difference in number of hospital admissions of frail older people that occur in the different seasons of the year. It suggests an increase in the winter months.

3.7. Associations of MRP with deterioration

In this study, hospitalisation was common to all patients exposed to MRPs (Prevalence 33.28%). The proportion of exposed patients with delirium, fall, NEWS ≥3 and deterioration score ≥ 2 with their respective relative risks (RR) are presented in Table 3. Frail older people with MRPs were three times more likely to suffer delirium than those without MRPs but chances of having more than one indicator of deterioration

Table 3
Relative Risk (RR) of deteriorating from MRPs

Patients' characteristics Indicators of deterioration	With MRPs	Without MRPs	Relative Risk (RR)	95% CI for RR Lower Upper
Delirium	18 (6.0%)	6 (2.0%)	2.970	1.196 7.378
Fall	80 (26.7%)	90 (30.3%)	0.880	0.682 1.135
NEWS ≥3	114 (38.0%)	137 (46.1%)	0.824	0.681 0.996
Deterioration (score ≥ 2)	149 (49.7%)	173 (58.2%)	0.853	0.735 0.990

(deterioration score ≥ 2) per case was similar for both groups (RR 0.853).

3.8. Medicines implicated in MRPs

Top ten classes of medicines implicated in medicines related problems in order of common occurrence across MRPs were, diuretics (63), opioids (37), oral hypoglycaemic (24), angiotensin converting enzyme inhibitors (ACEi) (23), betablockers (21), calcium channel blockers (21), insulins (13), antipsychotics (10), non-steroidal anti-inflammatory drugs (NSAIDs) (9), and warfarin (8).

4. Discussion

Prevalence of MRPs among frail older people admitted to hospital from Primary care including care and own homes was 33.28%. Delirium was associated with MRPs with a relative risk of 2.970. Types of MRPs were ADR (20%), non-compliance (9.1%), unintentional poisoning (3.3%), and inappropriate polypharmacy (0.8%). The significant predictors of MRPs were, presence of PIM, having no social support, and number of comorbidities.

Number of indicators of deterioration was similar in group with MRPs and in group without MRPs. However, more people deteriorated with delirium in group with MRPs compared to group without MRPs. Though this study did not investigate association of different groups of medicines with deterioration or its indicators such as delirium and this can be viewed as a limitation, it showed three classes of medicines that were most implicated in MRPs as medicines for the cardiovascular system including furosemide, bisoprolol, indapamide and lercanidipine, medicines for the nervous system which were codeine, buprenorphine, citalopram, meptazinol, and medicines for the endocrine system including prednisolone, insulin aspart, metformin and insulin glargine. Similarly, a systematic review[29] identified psychoactive medicines, antidepressants, betablockers and nifedipine as preoperative agents associated with postoperative delirium. Furthermore, a large cohort study showed that delirium was 20 times higher in people on beta-blockers than those on calcium channel blockers. Although these studies were on dissimilar patient groups, the findings suggest similar trajectory of relationship between certain classes of medicines and outcome delirium.[30]

Similar to other studies which have found amitriptyline to be associated with delirium, this study identified amitriptyline which is a psychoactive tricyclic antidepressant as a PIM in this cohort of patients. A surveillance study undertaken in German speaking countries, identified amitriptyline as the second (second to clozapine) most causally associated medication in drug induced delirium.[31] Strong affinity to muscarinic receptors and having anticholinergic properties makes amitriptyline a medicine of risk for delirium.[31]

The significance of identifying medications that are associated with medication induced delirium is that such episodes of delirium can be reversed by discontinuing, deprescribing or reducing dose of implicated medicines.[32]

Higher prevalence of MRPs (33.28%) was identified by this study than was reported by previous studies on hospitalisation from MRPs (5.6%[33]–6.55%[34]). This suggests that frail older people in primary care have high vulnerability to MRPs[35] which can sometimes result in hospitalisation. It is worth noting that because of the poor agreement among members of the external panel of assessors for validity of the causality tool, the research team adopted a cautious approach in labelling hospitalisation of the 33.28% that had MRPs as being caused by MRPs.

Being on 11 or more medicines was a risk factor for MRPs for these patients. Although when this risk was investigated with other variables in multivariate regression analysis, its contribution was not statistically significant, it's risk should not be disregarded. This is because findings from previous studies also showed risk of medicines to be increased with increase in number of medicines taken.[36] Hence, the importance of safe deprescribing in frail older adults cannot be over emphasized.[37,38]

There was a difference in the number of hospital admissions among frail older adults occurring in the different seasons of the year. The winter months showed higher number of admissions when compared to the spring and the summer months respectively. However, caution in attributing this to MRPs is advised till more studies can ascertain this. A recent systematic review also identified time of the year as a factor in MRPs.[39] There is evidence of personal and other vulnerability factors for seasonal variations of diseases, with the colder winter months having higher incidence of occurrence than the other months.[40] It is possible that with a high incidence of diseases in the winter months, frail older adults are exposed to an increase in number of medicines, inappropriate polypharmacy and MRPs. It will be interesting to investigate how seasonal variations can influence the trajectory of MRPs. MRPs interventions can be intensified during that season.

Similar to this study's findings that having no social support was associated with MRPs, a literature review of medicines related problems in people of ethnic minorities, identified lack of social support as a factor in MRPs.[41] Another systematic review identified social support as a positive factor in medication adherence.[42] The implication of this is that social support is a factor in medicines related problems.

Social support is an important factor in the health care of frail older adults since a frail older patient with social support would be more likely to visit a healthcare setting when deteriorating than one without social support. Furthermore, presence of social support for frail older people can indicate dependency which has been associated with MRPs.[43,44] Knowledge of association between dependency and MRP underscores the need to monitor medication use in this group of adults in order to maintain medication safety.

The identification of predictors or risk factors for MRPs in frail older adults through multivariate analysis was necessary to avoid confounders biasing effect of MRPs on deterioration. Hence, the multivariate model indicated that age and frailty were not significant risk factors for MRPs. It was beyond the scope of this work to investigate the impact of varying age groups and levels of frailty on MRPs. However, it would be interesting for future studies to undertake this.

One of the positives of this study is that MRPs associated hospitalisations confirmed with explicit WHO-ICD10 tool were first identified by doctors through implicit clinical knowledge during routine clinical practice.[43] Despite poor agreement among independent assessors who assessed this during the study on causality of MRPs for deterioration/hospitalisation, possibility of a strong relationship is clear and will benefit from future surveillance study. Furthermore, poor agreement among the assessors for this study suggests that in undertaking research, subjective inclination or conviction can play a role while applying an objective tool (WHO-UMC) in retrospective decision making. In addition, this finding of a level of disagreement between perceived causality of outcome at routine clinical practice and research respectively exhibits a level of dissonance that can exist between practice and research.[45]

Research of MRPs in this study adopted a unique approach. In this approach MRPs were identified by healthcare professionals in the course of their work, classified with a global tool-WHO-ICD10 by workers trained and skilled in the art, and certified by researchers who were pharmacists. These researchers being pharmacists were able to apply intrinsic clinical pharmacy knowledge, extrinsic WHO-ICD10, BNF, and EMC to the process, making it robust and reliable. It is evident from this study, that with collaborative efforts, MRPs can be reliably identified and classified in the course of clinical practice.

Finally, it is important to note that identifying delirium as a significant indicator of deterioration in this study, underscores the importance of assessing deteriorating frail older patients for delirium. This is currently a routine practice in the UK. This is an important call, given that mortality can increase by up to 11% for every 48 h there is active delirium.[46]

4.1. Limitations

The study cohort was mostly people aged ≥75 although the intended population was those aged ≥65, this was because frailty was routinely assessed for people aged 75 years and over at the time of the study. Furthermore, this study was carried out in a largely affluent part of the East of England hence the result may have a limited generalisation. Finally, there was a 15% (94 out of 600) loss of participants' data from the calculated sample size but assuming this as participants drop out, it was within the allowed follow up threshold of 60–80%.[47]

5. Conclusion

This study combined physiological, cognitive, and physical deterioration to achieve a concept of deterioration in frail older people with MRPs. No other study had done this. One of the important outcomes in terms of knowledge of medication safety is that frail older adults exposed to MRPs have higher risks of deteriorating with delirium than patients not exposed. Furthermore, this study shows that researching data collected by experts for routine clinical purposes, as was the case here can provide useful insights on medication related problems and deterioration from them. As data was obtained through a systematic review of patients' records and indicators of deterioration are relatable to older people, it provides scale of harm of MRPs in frail older patients. In addition, identification of MRPs at the point of patients' admission which was carried out by secondary care junior doctors and subsequently confirmed by hospital consultants, enhanced reliability, and validity of the research findings.

Finding on social support implies that living with a partner or presence of a caregiver can minimize the occurrence of MRPs in frail older adults.

In addition, since ongoing hospital care or hospitalisation indicates or suggest deterioration from MRPs in frail older adults, it is important to investigate the interaction between features of deterioration, frailty and MRPs in patients. This lies outside the scope of this study but can be undertaken for future studies.

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CRediT authorship contribution statement

Rosetta Chinyere Ude-Okeleke: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Zoe Aslanpour:** Conceptualization, Methodology, Project administration, Supervision. **Soraya Dhillon:** Conceptualization, Methodology, Project administration, Supervision. **Nkiruka Umaru:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Rachel Berry:** Data curation, Methodology, Writing – review & editing. **Emma Bines:** Data curation, Methodology.

Declaration of Competing Interest

There is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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