Identifying medication-related hospital admissions in older patients with polypharmacy and 2 or more triggers of the triggerlist: a retrospective study

Research Project master Pharmacy

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Abstract (ENG)

Background

Previous studies have shown that between 10 and 30% of hospital admissions in older patients is medication-related. The triggerlist is used in emergency departments to help physicians recognize medication-related problems. This study aimed to investigate whether the triggerlist is an efficient tool for the selection of older patients with polypharmacy who have a *possible* medication-related admission based on the AT-HARM10 tool.

Method

A retrospective study was conducted in Zuyderland Medical Centre, Sittard-Geleen, the Netherlands. The AT-HARM10 tool was used to assess whether the unplanned hospital admissions of the first 100 patients included in the CHECkUP study were *possibly* or *unlikely* medication-related. Furthermore, the Charlson Comorbidity Score, number of medications prior to the index admission, renal function, number of trigger diagnoses and number of medications which causes trigger diagnoses were compared between patients with a *possibly* MRA or an *unlikely* MRA.

Results

48.5% of hospital admissions were identified as *possibly* medication-related. Decreased renal function (eGFR) was significantly associated with a higher risk on *possibly* medication-related admissions (p=0.015). Renal function eGFR<30 increases the risk on *possibly* MRA in comparison with a renal function eGFR 30-50 (OR 5.3 (CI 1.4 – 19.6)) and eGFR >51 (OR 4.3 (CI 1.4 – 13.5)). There was no significant association between number of medications, CCI-score, number of trigger diagnoses and number of medications which causes trigger diagnoses.

Conclusion

MRAs are prevalent in older patients who had polypharmacy and at least 2 trigger diagnosis on the triggerlist. The triggerlist seems to be an efficient tool for the inclusion of patients with a high risk on *possibly* medication-related admissions.

Keywords: medication-related hospital admission, elderly, polypharmacy, triggerlist

Samenvatting (NL)

Achtergrond

Onderzoek heeft aangetoond dat 10 tot 30% van de ziekenhuisopnamen bij ouderen medicatie-gerelateerd is. De triggerlijst is een hulpmiddel voor artsen om op de spoedeisende hulp medicatie-gerelateerde problemen te herkennen. Dit onderzoek heeft als doel te onderzoeken of de triggerlijst een geschikt hulpmiddel is voor de selectie van ouderen met polyfarmacie die een *mogelijke* medicatie-gerelateerde ziekenhuisopname hebben gebaseerd op de AT-HARM10 tool.

Methode

Er is een retrospectief onderzoek uitgevoerd in Zuyderland Medisch Centrum te Sittard-Geleen, Nederland. De AT-HARM10 tool is gebruikt om te beoordelen of de ongeplande ziekenhuisopnamen van de eerste 100 geïncludeerde patiënten in de CHECkUP studie *mogelijk* of *onwaarschijnlijk* medicatie-gerelateerd waren. Daarnaast is de Charlson Comorbidity Score, aantal medicamenten vóór opname, nierfunctie, aantal trigger diagnosen en aantal medicamenten die trigger diagnosen veroorzaken vergeleken tussen patiënten met een *mogelijk* medicatie-gerelateerde ziekenhuisopname en *onwaarschijnlijk* een medicatie-gerelateerde ziekenhuisopname.

Resultaten

Van de ziekenhuisopnamen werd 48.5% beschouwd als *mogelijk* medicatie-gerelateerd. Verminderde nierfunctie (eGFR) was significant geassocieerd met een hoger risico op *mogelijk* medicatie-gerelateerde opnames (p=0.015). Een nierfunctie eGFR<30 verhoogt het risico op een medicatie-gerelateerde opname in vergelijking tot een nierfunctie eGFR 30-50 (OR 5.3 (CI 1.4 – 19.6)) en eGFR >51 (OR 4.3 (CI 1.4 – 13.5)). Er werd geen significant verschil gevonden in het aantal medicijnen, CCI-score, aantal triggerdiagnosen en het aantal medicijnen dat de triggerdiagnosen veroorzaakt.

Conclusie

Medicatie-gerelateerde opnamen komen vaak voor bij ouderen met polyfarmacie en tenminste twee triggerdiagnosen van de triggerlijst. De triggerlijst lijkt een efficiënte tool voor de inclusie van patiënten met een hoog risico op *mogelijk* medicatie-gerelateerde opnamen.

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List of abbreviations

MRA	Medication-Related Admission
MRP	Medication-Related Problem
ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
CDSS	Clinical Decision Support System
CRR	Clinical Rule Reporter
ED	Emergency Department
AT-HARM10	Assessment Tool for Hospital Admissions Related to Medications
CHECkUP	Control in the Hospital by Extensive Clinical rules for Unplanned hospitalisations in older Patients
CCI	Charlson Comorbidity Index
INR	International Normalized Ratio
ATC	Anatomical Therapeutic Chemical

1. Introduction

Polypharmacy, the chronic use of five or more medications from different therapeutic groups or subgroups [1], increases the risk of medication-related hospital admissions (MRAs). [2] According to Kempen et al. [3] a medication-related admission is a hospital admission where the medication-related problem (MRP) is the main cause or a significantly contributing cause for a hospital admission. Without the MRP, the patient would not have been admitted. [3] MRPs are defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome. [3-7] MRP comprises a broader set of possible problems that not only includes adverse drug reactions (ADR). Besides ADRs, MRPs can also involve medication-errors. Examples of medical errors are inappropriate prescribing in which the patient is sub-optimally treated, and non-compliance, in which the patient does not use the medication appropriately. [3,5,8,9]

Because there is a large variability in the used definitions for MRAs, there is a wide range of incidences.[10] In addition, study design and inclusion criteria like age are different between studies, which causes heterogeneity. [8,11] However, 10-30% of hospital admissions in older patients are because of adverse drug events, which includes ADRs and medication-errors. [8,9,12,13] Because MRP comprises a broader definition than adverse drug events (ADE) and a lack of identification, a higher incidence number of MRP and thus MRA is expected. [10]

Older patients often have several comorbidities which contribute to a higher risk on hospital admissions. [14] This increased risk may partially be due to a higher number of chronic used drugs. Furthermore, pharmacokinetic and pharmacodynamic changes which occur in older patients increase the risk of medication-related problems. [15] In order to reduce this risk, the Dutch multidisciplinary guideline ''Polypharmacy in Elderly'' recommends a medication review for these patients. [1] However, a study by Christensen et al. found no evidence that medication reviews reduces mortality or hospital readmissions.[16] Furthermore, medication reviews are time-consuming and their frequency is usually low. In the period between medication reviews, impairment of organ function, alterations in medication and/or additional comorbidities can occur. Therefore, De Wit et al. developed an advanced clinical decision support system (CDSS), the Clinical Rule Reporter (CRR). [17] This computer system could help physicians and pharmacists by performing medication reviews. The CDSS will generate alerts for the inappropriate combination of medication, laboratory values and comorbidities. By using a CDSS continue monitoring of the medication list is feasible instead of a less frequent medication review. In the CHECkUP study there will be examined whether the amount of hospital readmissions in older patients will be reduced by a weekly, extensive medication screening using a CDSS. [18]

For the inclusion of patients in the CHECkUP study [18], the triggerlist as proposed by the Dutch guideline ''Polypharmacy in the older patient'' is used. [1] See appendix 1. This triggerlist has been developed to recognise patients with a MRP at the emergency department (ED). [1,11]

In this study, a standardized method will be used to identify MRAs of patients included in the CHECkUP study. [18] A standardized method can minimize subjectivism in comparison to assessments only by an expert panel consisting of pharmacists and physicians. Many studies use validation tools like the Naranjo scale [19], WHO-UMC [20], Hallas criteria [21] and Kramer algorithm. [22] However, these tools are developed to measure ADRs instead of MRPs. Using one of these tools to identify ADRs, will lead to an underestimation of the amount of MRPs.

In contrast to the methods mentioned above, both the Assessment Tool for Hospital Admissions Related to Medications (AT-HARM10 tool)[3] and the Drug Related Admission (DRA) adjudication guide[23] identify MRAs in older patients. The DRA-adjudication guide is time-consuming (approximately 23 minutes for each assessment) and an expert panel is required. Also, this tool is not yet validated for

the predictive validity, sensitivity and specificity to detect MRAs. [23] Therefore, in this study the number of MRAs of patients aged 60 years and older with polypharmacy and at least two trigger diagnoses of the triggerlist who were unplanned admitted in the hospital will be determined according the AT-HARM10 tool.

AT-HARM10 includes all relevant categories of MRPs and is a valid and practical tool to identify MRAs in older patients. [3,6] In addition, an assessment takes on average 6 (range 2.5-14) minutes. [3] However, it was unclear if the tool could be used in other countries than Sweden. Therefore, two Dutch 5th year pharmacy-students investigate application of this tool and conclude Dutch students are able to use AT-HARM10 without using an expert panel consisting of senior clinicians or pharmacists. They could identify 80% of MRPs. [24]

The aim of this research is to investigate whether the triggerlist is an efficient tool for the selection of older patients with polypharmacy who have a *possible* medication-related admission based on the AT-HARM10 tool.

2. Methods

2.1 Study design

This retrospective study was conducted in Zuyderland Medical Centre, Sittard – Geleen (the Netherlands) and is part of the CHECkUP study. [18] CHECkUP means Control in the Hospital by Extensive Clinical rules for Unplanned hospitalisations in older Patients and is a randomised controlled trial where the intervention consists of an extensive weekly medication screening using a CDSS. The CDSS will not be performed in the control group. The aim of the CHECkUP study is to reduce the number of hospital readmissions in older patients (≥60 years) from 20% to 15% within one year.

All patients in this substudy of CHECkUP were admitted to the hospital between March and October 2019.

2.2 Study-population

The CHECkUP study included patients aged 60 years and older, with polypharmacy (≥ 5 chronic medications) who are able to give informed consent and using medications which lead to at least 2 trigger diagnoses from the triggerlist as proposed by the Dutch guideline ''Polypharmacy in the older patient''. [1] They were included during their first unplanned hospitalization after the start of the inclusion period. All patients were admitted at Zuyderland MC location Sittard-Geleen. Exclusion criteria were a planned admission, admission because of intentional intoxication, use of oncolytic in the past three months, a life expectancy below three months and living in a dependent living situation, like a nursing home.

In this substudy of the CHECkUP, the first 100 included patients of the CHECkUP study were included. In addition, patients who have been admitted to Zuyderland MC from another hospital during one admission were excluded, because there is no access to their medication list prior to the index-admission.

2.3 The AT-HARM10 and the application

The AT-HARM10 tool is a questionnaire consisting of 10 questions, comprising of MRPs, which can be answered with yes or no. See appendix 2 for the tool. [3] The first three questions are used to identify admissions that are *unlikely* to be medication-related by answering 'yes' to any of these questions, while question 4-10 are used to identify admissions that are *possibly* medication-related by answering 'yes' to any of these questions. When one of the ten question is answered with 'yes', the assessment is finished. When all questions were answered with 'no', an expert panel of clinical pharmacists is needed. It is difficult to conclude whether an hospital admission is certainly medication related. Therefore, in agreement with the developers of the AT-HARM10 tool, in this article there will be spoken of *possibly* and *unlikely* medication-related admissions.

Prior to the start of applying the tool on the first 100 included patients in the CHECkUP study, the researchers (MJ, LP, AL and VM) read the instructions for use and the examples supplemented to the AT-HARM10 tool. [3] After that, the supervisors randomly selected six training cases for the student researcher (MJ) to practice with the tool. The results were discussed with a general pharmacist specialized in medication reviews (LP) and a resident clinical geriatrics. Also, the results of the training cases were discussed with the researchers of the Uppsala University who developed the AT-HARM10 tool. Furthermore, some additional questions and uncertainties were discussed with the Swedish researchers.

The student researcher (MJ) used the admission letter, medication list upon admission, laboratory data during hospital stay and the discharge letter to apply the AT-HARM10 tool. This information was

obtained from the hospital electronic information system. All information above was collected in a secure and anonymized document.

For all included patients the student researcher (MJ) assessed whether the index admission was either *possibly* or *unlikely* medication-related according the AT-HARM10 tool. The index admission was the same admission in which the patients were included for the CHECkUP study. The general pharmacist (LP) specialized in medication reviews who was also involved by the training cases independently assessed the index admissions based on the information collected by the student researcher (MJ). Discrepancies between student researcher (MJ) and general pharmacist (LP) were independently assessed by a geriatrician (AL) and a hospital pharmacist (VM) who also used the medical information collected by the student researcher (MJ). After that, all discrepancies were discussed with the entire team to reach a consensus whether the cases were *possibly* or *unlikely* medication-related. A senior professor clinical pharmacologist/ hospital pharmacist (HvdK) participated in this meeting.

2.4 Outcome measures

The primary endpoint of this study is the number of *possibly* medication-related admissions in unplanned hospital admissions of older patients with polypharmacy and at least two trigger diagnoses on the triggerlist according the AT-HARM10 tool. Secondary endpoints were the number of medications prior to the index admission, Charlson Comorbidity Score (CCI) [25], renal function, number of trigger diagnoses and number of medications which induce trigger signals based on Anatomical Therapeutic Chemical (ATC) codes.

As a measure of the patients' comorbidities, the CCI score was used. This score was calculated by collecting information stated in the hospital medical record at the time of index admission. This score was not corrected for age, because age was measured separately in this study. The International Classification of Diseases and Related Health Problems (ICD)-10 algorithms of each 17 Charlson comorbidities of Quan et al. [26] were used to calculate the CCI score. Comorbidities registered during index admission were not included by calculating the CCI score.

The number of medications prior to index admission was calculated using information from the hospital medical record. Patients were categorized in using 0-4 medicines, polypharmacy (5-9) and hyper polypharmacy ≥ 10 medicines. [27]

Renal function (eGFR (ml/min/1.72m^2)) was measured between 3 clinically relevant categories: eGFR <30; eGFR 30-50 and eGFR ≥51.

The number of trigger diagnoses and the number of medicines which induces triggers were manually calculated using the triggerlist and the medication list of each patient.

Department of hospital stay was categorized in two groups, surgical and medical specialisms. Surgical specialisms consists of surgery, orthopedics and urology. Geriatrics, Internal medicine, pulmonology, gastroenterology, neurology and oncology were categorized as medical specialism.

2.5 Statistical analysis

Statistical analysis was performed using IBM. SPSS version 27.0. The sample size is calculated using the confidence interval for a proportion by expecting a number of MRAs of 10-15%, the 95% confidence level is 0.0516 – 0.1804 or respectively 0.0891-0.2385.

The number of *possible* MRAs was reported using descriptive statistics. Categorical variables were presented using numbers and percentages (%). These variables were analyzed using Pearson $\chi 2$ test or Fisher exact test when the number of cases was ≤5. Continue variables, i.e. age, CCI score, number of medications were presented using the mean and standard deviation [SD] for normally distributed.

Continue variables were analyzed using independent sample t-test. P-values < 0.05 were considered statistically significant.

3. Results

3.1 Patient characteristics

102 patients were screened for this study. 2 patients were excluded because they were admitted to Zuyderland MC from another hospital during one admission. The mean age of the included patients was 75.2 years (range 60-95, SD 8.6) and 45 patients (45%) were female. The median CCI score was 2.2 (range 0-8, SD 1.5) and the median number of medicines prior to index admission was 10.7 (range 2-25, SD 4.5). Table 1 describes the baseline characteristics of the included patients.

Table 1. baseline characteristics of older patients with polypharmacy during index admission

Variable	All admissions	MRA *possibly* (n= 48)	MRA *unlikely* *(n= 51)*	P value
Sex: n (%)				0.787
Female	44 (45)	22 (22)	22 (22)	
Male	55 (55)	26 (26)	29 (29)	
Age at admission, (years) n(%) :				0.443
60-74	43 (43.4)	22 (45.8)	21 (41.2)	
75-89	52 (52.5)	23 (47.9)	29 (56.9)	
≥ 90	4 (4.0)	3 (6.3)	1 (2.0)	
Mean ± SD	75.2 ± 8.6	74.7 ± 9.0	75.8 ± 8.2	0.504
Range min-max	60-95			
Charlson Comorbidity Index Score (%) :				0.110
0	11 (11.1)	3 (6.3)	8 (15.7)	
1-2	52 (52.5)	24 (50.0)	28 (54.9)	
3-4	31 (31.3)	16 (33.3)	15 (29.4)	
5-6	4 (4.0)	4 (8.3)	0 (0.0)	
≥7	1 (1.0)	1 (2.1)	0 (0.0)	
mean ± SD	2.2 ± 1.5	2.4 ± 1.6	2.0 ± 1.2	0.136
Range min-max	0-8			
Renal function, eGFR (ml/min/1.73m²), n (%)				0.015
0-29	21 (21.2)	16 (33.3)	5 (9.8)	
30-50	24 (24.2)	9 (18.8)	15 (29.4)	
≥ 51	54 (54.5)	23 (47.9)	31 (60.8)	
Number of medicines at index admission, n (%)				0.407
0-4	4 (4.0)	1 (2.1)	3 (5.9)	
5-9	43 (43.4)	19 (39.6)	24 (47.1)	
≥10	52 (52.5)	28 (58.3)	24 (47.1)	
Mean ± SD	10.7 ± 4.5	10.9 ± 4.3	10.5 ± 4.7	0.641
Range min-max	2-25			
Trigger diagnoses				0.962
0-2	13 (13.1)	6 (12.5)	7 (13.7)	
3-5	43 (43.4)	21(43.8)	21 (43.1)	
≥6	43 (43.4)	21 (43.8)	23 (43.1)	
Mean ± SD	5.0 ± 1.9	5.0 ± 1.8	5.0 ± 2.0	0.920
Trigger medications				0.911
0-2	21 (21.2)	10 (20.8)	11 (21.6)	
3-5	45 (45.5)	21 (43.8)	24 (47.1)	
≥6	33 (33.3)	17 (35.4)	16 (31.4)	
Mean ± SD	4.4 ± 2.2	4.5 ±2.2	4.4 ± 2.3	0.780

SD: Standard Deviation

3.2 Outcomes AT-HARM10 tool

In total, the student researcher (MJ) and the general pharmacist (LP) assessed 100 admissions. They had an agreement of 64% of the assessments. Of these, 35 were identified as *possibly* medication-related and 29 admissions as *unlikely* medication-related. After discussing the admissions where there was a disagreement with the multidisciplinary team, 13 admissions were assessed as *possibly* medication-related and 22 admissions as *unlikely* medication-related. 1 admission could not be assessed because the multidisciplinary team did not reach consensus on the outcome.

Finally in total, 48 hospital admissions were assessed as being *possibly* medication-related (48.5%). An illustration of these results is shown in figure 1.

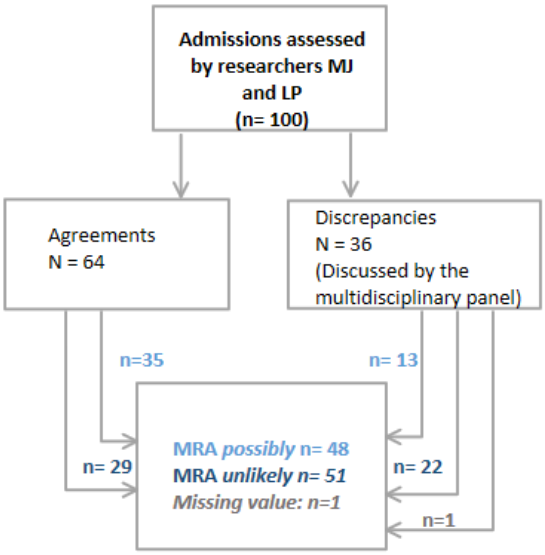

Figure 1. Number of *possibly* and *unlikely* medication related hospital admissions according AT-HARM10

Table 2 shows the frequency of questions of the AT-HARM10 tool which are used to assess the 48 admissions as *possibly* medication-related. Half of the *possibly* medication-related admissions was caused by side-effects or over-treatment. In 20.8% of the *possibly* MRAs, the medical record hinted or stated that the admission was medication-related. 9 admissions were assessed as *possibly* medication-related because the patient did not receive treatment or was sub optimally treated for a previously diagnosed disease.

Table 2. Categorization of answered questions of the AT-HARM10 tool

Question 4-10 of the AT-HARM10 tool[3]	**Number of MRAs, n (%)**	**Example**
P4 is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?	10 (20.8)	Nausea and vomiting since the use of tramadol. After discontinue tramadol, patient recovered well clinically.
P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including over-treatment)?	24 (50.0)	Bradycardia, probably because of sotalol accumulation caused by acute renal dysfunction.
P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission?	2 (4.2)	Increased INR (7.6) by use of acenocoumarin.
P7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?	1 (2.1)	Contra-indication metoprolol and AV-block
P8. Did the patient have any previously diagnosed untreated or sub-optimally treated (e.g. dose too low) indications that might have caused the admission?	9 (18.8)	Patient was admitted because of oedema. Bumetanide dosage was not increased unless his weight gain of 10kg in 1 month.

P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?	1 (2.1)	Dyspnea after switch between inhalator. Probably fail of inhalation technique.
P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?	1 (2.1)	After discontinue of prednisolone immediately increase of dyspnea. There was no drug withdrawal schedule.

3.3 Secondary endpoints

Age and gender did not significantly differ between patients with an *possibly* or *unlikely* MRA.

There was no statistically significant difference in the number of medicines prior to the index admission between the two groups.

The CCI score was not significantly associated with the occurrence of *possibly* MRAs (p=0.110). Furthermore, the mean CCI score for patients with a *possibly* MRA did not significantly differ from the mean CCI score for patients who *unlikely* had an MRA (p=0.136)

Renal function (eGFR) was significantly associated with a higher risk on *possibly* medication-related admissions (p=0.015). Renal function eGFR<30 increases the risk on *possibly* MRA in comparison with a renal function eGFR 30-50 (OR 5.3 (CI 1.4 – 19.6)) and eGFR >51 (OR 4.3 (CI 1.4 – 13.5)).

The number of trigger diagnoses related to ATC-codes of de medication prior to the index admission, derived from the triggerlist did not significantly differ between the two groups. The number of medications that causes trigger diagnoses was also not significant associated to the occurrence of *possibly* MRAs.

Of all admissions, 16 patients were admitted on surgical departments and 83 patients were admitted on diagnostic departments. There was no significant association between these two categories on the outcome of the AT-HARM10 tool.

4. Discussion

In this cohort of older patients (≥ 60 years) with polypharmacy and ≥2 triggers, 48% of hospital admissions were defined as *possibly* medication-related.

To our knowledge the CHECkUP study [18] is the first study that uses the triggerlist from the Dutch guideline ‘‘Polypharmacy in the older patient’’ [1] for the inclusion of patients. By selecting patients with at least two trigger diagnoses based on their medication list a cohort of patients with a higher risk on *possibly* MRAs could be reached. This could be an explanation for the high prevalence of *possibly* MRAs in this study. Furthermore, in the CHECkUP study, all patients had polypharmacy, a known risk factor for MRA. [2,28,29] With the inclusion criteria of polypharmacy, the triggerlist and older patients, the researchers of the CHECkUP study wanted to select a cohort of patients with a high risk for MRAs.

Other studies which also select patients with a higher risk for MRAs are for example the studies of Lea et al [30] and Zerah et al. [31] Both studies choose to select on multimorbidity, defined as the presence of at least two conditions. [32] Lea et al. [30] included patients with ≥4 medications of at least 2 ATC groups at 1st level at admission as surrogate of multimorbidity and Zerah et al. [31] choose to include patients who had ≥3 chronic medical conditions and polypharmacy. The mean age of included patients was 79 years in both studies. These two studies of Lea et al. [30] and Zerah et al. [31] found respectively a prevalence of MRAs of 38% and 42%. These results are in line with our study and this suggests adding

multimorbidity, polypharmacy and at least two trigger diagnosis of the triggerlist could possibly contribute to select a cohort with a higher prevalence of *possibly* MRAs.

Previous studies found incidences of MRAs varying between 5.6% and 30% in adult patients without any risk factors. [2,9,12,13,33] When specifically focusing on European studies with older patients, a recent meta-analysis found an incidence of MRAs of 10%. [13,33] These studies did not specifically select older patients, patients with polypharmacy and patients with at least 2 triggers of the triggerlist. Because the CHECkUP study adds this selection criteria to the cohort, this could explain the higher percentage of MRAs in this study.

We did not find any significant associations between gender, age, number of medications, CCI score, number of trigger diagnoses and number of trigger medicines and the occurrence of *possibly* MRAs. An explanation for the fact we did not find a significant association between the number of medications and *possibly* MRAs is that in the CHECkUP study, only older patients (≥60 years) with polypharmacy and ≥2 triggers were included. For that reason, in this study, the number of patients using <5 medicines is minimal and not sufficient to demonstrate an significant association. This is in agreement with Lea et al. [30] where patients were included when using a minimum of four medicines. They also found no significant association between number of medicines and MRAs. Other studies that not have polypharmacy as an inclusion criterium, all concluded that polypharmacy is a risk factor for the occurrence of MRAs. [2,28,29] CCI score was not significant associated with the occurrence of MRAs. It could be possible that our sample size is too small to demonstrate an association. In addition, we did not perform a multiple regression analysis. However, our findings are again in agreement with the results of Lea et al [30] who also found no significant association between CCI score and the occurrence of MRAs. A possible explanation for this could be that when all patients included in the study have ≥2 triggers or multimorbidity, their CCI score will be higher in contrast to study populations without these inclusion criteria. Renal impairment (eGFR <30) is significant associated with a higher risk on *possibly* MRAs in comparison with eGFR ≥ 30. This result is in agreement with the study of Leendertse et al [2] and Cabré et al. [28]

This study has several limitations. First, in the CHECkUP study patients were included when their medication list had two or more trigger diagnosis on the triggerlist. However, the medication list used in the CHECkUP study consist of the medicines used during index admission. This list could differ from the medications prior to the index admission. Therefore, the student researcher manually calculated the number of trigger diagnosis. Because of this, some patients had <2 trigger signals and used <5 medications prior to the index admission, but were still included in the CHECkUP study. Otherwise, there is a possibility the CHECkUP study missed patients who used 5 or more medications before index admission, but did not used them during the index admission and therefore were not included in the CHECkUP study. Second, because we evaluated the hospital admissions retrospectively, we were dependent on the amount of information in the hospital electronic information system. Therefore, our assessment was made on the medical information registered by other physicians. In addition, in most cases we had no information about over-the-counter drug use and compliance. Non-compliance could lead to a *possible* MRA. Third, two investigators independently assessed all admissions and the discrepancies between them were discussed with a multidisciplinary team which reduces the risk of error. However, their assessments were possibly biased because they are based on the information the student researcher noted from the hospital electronic information system. The most important reason for this was that obtaining the medication list prior to the index admission was time-consuming. Fourth, we calculated the CCI score by using the information of the hospital electronic information system. This information is not always complete or up to date. Therefore, the actual CCI score is probably higher. At least, this was the first time for all researchers to work with the AT-HARM10 tool.

The multidisciplinary panel did not reach consensus about one assessment. The geriatrician did not agree with the pharmacists. During the discussion of the discrepancies, we often observed that the geriatrician reasons from a more clinically perspective than the pharmacist's, which could lead to a different view on the assessments. Furthermore, during some assessments, we lack expertise, for example the knowledge of lung diseases.

Based on findings of this study and the other studies previously mentioned, we can recommend further investigation on the effects of adding the additional risk factors polypharmacy, multimorbidity and a minimum number of trigger diagnoses to the inclusion criteria of studies investigating the number of MRAs. By selecting a cohort with a higher risk on MRAs, previously investigated interventions on the reduction of MRAs may have a higher impact. Furthermore, patients with an impaired renal function have a higher risk of a MRA. We should therefore be aware of this fact by the prevention of MRAs.

5. Conclusion

In this cohort of older patients with polypharmacy and ≥2 trigger diagnosis on the triggerlist, 48% of hospital admissions were defined as *possibly* medication-related. Using this selection criteria will probably lead to a higher prevalence of *possibly* MRAs in comparison to cohorts who do not apply these inclusion criteria. The triggerlist seems to be an efficient tool for the inclusion of patients with a high risk on *possibly* medication-related admissions.

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Appendix 1

Triggerlist from the Dutch guideline ''Polypharmacy in the older patient'' [1]

Trigger (adverse clinical event)	**Often involved medication**
Fracture/fall	Psychotropic medication (falls) / corticosteroids/ antihypertensive drugs
Collapse/hypotension/dizziness	Cardiac medication (antihypertensive drugs and antiarrhytmics) / psychotropic medication
Bleeding (GI tract) / supratherapeutic INR	Anticoagulants Antiplatelet drugs NSAID
Electrolyte imbalance/ dehydration	Diuretics, ACEi, AII-blocker, NSAID, antidepressants
Renal insufficiency	ACEi, AII-blocker, NSAID
Hypo- or hyperglycemia	Insulin/oral antidiabetics Corticosteroids
Heart failure	NSAID
Obstipation / ileus	Opioids/ calcium blockers
Vomiting/ diarrhea	Antibiotics
Delirium/ confusion / drowsiness	Psychotropic medication/ cardiac medication/ medication for micturition complaints/ benzodiazepines

Appendix 2

AT-HARM10 tool [3]

U1. Was the admission caused by an infection or a previously undiagnosed disease (e.g. diabetes or heart failure) that is not medication-related?
U2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?
U3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?
P4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?
P5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalization have caused the admission (including over-treatment)?
P6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission?
P7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?
P8. Did the patient have any previously diagnosed untreated or sub-optimally treated (e.g. dose too low) indications that might have caused the admission?
P9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
P10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?