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Identifying older adults at increased risk of medication-related readmission to hospital within 30 days of discharge - development and validation of a risk assessment tool

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Older adults; Transitions in care; Patient discharge; Medication-related patient readmission; Risk factors; Risk assessment

ABSTRACT

Objective

To develop and validate a risk assessment tool aiming to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge.

Methods

The development cohort (n=720) was admitted to a hospital in the south of Sweden during 2017 whereas the validation cohort (n=892) was admitted to a hospital in the mid-eastern part of Sweden during 2017-2018. Variables known at first admission and individually associated with possibly medication-related readmission were used when developing the risk assessment tool. The included variables were assigned points and Youden's index was used to decide a threshold score. The risk score was calculated for all individuals in both cohorts. ROC-curves were plotted, and c-indexes were calculated as well as Hosmer and Lemeshow goodness-of-fit, Negelkerke R^2, sensitivity, specificity, and positive and negative predictive values.

Results

The developed 0-6 point risk assessment tool, the HOME Score, had a c-index of 0.69 in the development cohort and 0.65 in the validation cohort. Calibration was good in both cohorts. The risk score showed sensitivity 76%, specificity 54%, positive predictive value 29%, and negative predictive value 90% at the threshold score in the development cohort.

Conclusion

The HOME Score can be used to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. The tool is easy to use and includes variables that are available in electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in transitions of care. These activities could likely help increase patient safety and be beneficial to the health economy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The HOME Score is the first externally validated risk assessment tool aiming to identify older adults at increased risk of medication-related readmission to hospital within 30 days of discharge.
- According to previous studies, preventive measures aiming to reduce medication-related readmission should preferably include interdisciplinary actions during the hospital stay and at discharge as well as in transitions of care and follow-up. Therefore, only variables available in the electronic health records at admission are included in the HOME Score.
- Further validations of the HOME Score are needed in order to establish its clinical usefulness in different departments as well as in other countries.

INTRODUCTION

Readmission to hospital is common, especially in older adults where almost 20% of discharges result in a readmission within 30 days (1-3). In older adults, hospitalisation can be associated with a risk of complications such as exposure to infections, rise in adverse events, episodes of confusion, and accidental injury through falls (4, 5). As readmissions are not only a risk for the individual patient but also for the health economy (3), many countries have set goals to decrease the frequency of readmission within 30 days of discharge (3, 6, 7).

A relatively large proportion of readmissions of older adults are medication-related (8-10). Many of these medication-related readmissions may be possible to prevent, even though the proportion deemed preventable differs between studies (8). Preventive measures should aim to improve medication use as well as transitions of care (11, 12) and are best performed by combining several minor activities into concepts (12, 13). These activities should preferably include interdisciplinary actions during the hospital stay and at discharge (12) as well as collaboration between hospital, primary, and municipal care in transitions of care (14).

To effectively implement interventions, healthcare personnel need to be able to identify patients at increased risk of medication-related readmission. This could preferably be done by using a risk assessment tool or risk score (15). Some risk assessment tools linked to medication-related readmission have been developed (16, 17). The PRIME tool, developed by Parekh et al (16), identifies older adults at increased risk of medication-related harm requiring healthcare use within eight weeks of discharge while the decision support tool developed by Olson et al (17) predicts the risk of readmission in older adults using high-risk medication regimens. None of these tools have been validated in an external population or tested in a setting other than the one where it was developed.

To our knowledge, there is no risk assessment tool available that specifically aims to identify older adults at increased risk of possibly medication-related readmission to hospital within 30 days of

discharge. If such a tool was available, interventions aiming to prevent readmission could be implemented based on the risk in the individual patient (15). This could make it possible to not only increase patient safety but also relocate some resources to other areas within healthcare (18).

OBJECTIVE

The aim of this study was to develop and validate a risk assessment tool that can be used to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge.

METHODS

This study is reported according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement (15).

Setting

Sweden is divided into 21 regions and 290 municipalities (19). Primary and hospital care is provided by the regions while nursing care, in the community or in nursing homes, is provided by the local municipalities. When it comes to planning patient care after hospital discharge, hospital and municipal care are expected to collaborate (20).

According to Swedish regulations (21), medication reconciliation should be performed by the attending physician when patients aged 75 years and older using five medications or more are admitted to hospital. If medication-related problems are present, the medication reconciliation should be followed by a medication review which could or could not be performed interdisciplinary (i.e. involving a geriatrician or a clinical pharmacist). Unfortunately, adherence to these regulations

seems generally low (22) with only about 15% of patients aged 75 years and older receiving a medication reconciliation and/or medication review during their hospital stay (22).

Patient and public involvement

Patients or the public were not involved in this study.

Development of the risk assessment tool

The risk assessment tool was developed using anonymised data and results from our previously published retrospective studies (10, 23) where further details on the methods of data collection can be found.

Study sample and procedure

The study was conducted at Kristianstad hospital, which is an emergency hospital with 255 beds situated in Skåne county in the south of Sweden. The study population, which is further referred to as the development cohort, consisted of randomly selected patients (n=720), aged 65 years and older, who had been admitted to Kristianstad hospital for at least 24 hours in 2017. Patients were admitted to one of the following departments: internal medicine, infectious disease, general surgery, orthopaedics, or ear/nose/throat. The study group (n=360) was readmitted within 30 days of discharge while the comparison group (n=360) was not. Variables were collected from electronic health records in an unblinded yet standardised and objective manner, as previously described (23).

In total 143 of 360 readmissions (39.7%) were assessed as being possibly medication-related (10). Assessments were made using the Assessment Tool for identifying Hospital Admissions Related to Medication (AT-HARM10), a validated tool to distinguish between admissions that are possibly and unlikely medication-related (24). With AT-HARM10 a possibly medication-related (re-)admission is defined as being either caused by or significantly contributed to by a medication-related problem (for further details see Appendix 1). Preliminary assessments, made by the first

author in an unblinded fashion, were reviewed, revised, and finalised by an experienced geriatrician. For further details on the assessment process see our previous publication (10).

Through multiple logistic regression analysis (stepwise backward) individual risk factors associated with all-cause readmission, possibly medication-related readmission, and unlikely medication-related readmission within 30 days of discharge were identified, as described in our previous publications (10, 23).

Variables included

The risk assessment tool was developed using variables identified by comparing patients with a possibly medication-related readmission (n=143) with those that did not have a possibly medication-related readmission (n=577) (i.e. patients with an unlikely medication-related readmission (n=217) and patients not readmitted (n=360)). Only variables known at first admission to hospital were included in the development of the risk assessment tool.

Variables shown to be associated with possibly medication-related readmission, through multiple logistic regression analysis, were chosen to be included in the final risk assessment tool. For continuous variables, categorical variables were created based on comparisons between groups.

Data analysis

Based on the odds ratios of the individual variables in the final multiple logistic regression model, suitable weighting and scoring were decided upon for each of the included variables. A risk score, which summarised the points assigned to each of the variables included, was calculated for all the included individuals. Finally, a new logistic regression analysis was performed with possibly medication-related readmission as the dependent variable and the risk score as the test variable, saving the probabilities for further analysis. To estimate the quality of the model Hosmer and Lemeshow goodness-of-fit was calculated as well as Negelkerke R^2.

A ROC-curve was plotted using the saved probabilities and the area under the ROC-curve (c-index) was calculated giving a measure of how well the tool predicts possibly medication-related readmission.

To decide upon a suitable threshold value in the risk assessment tool Youdens' index (J = Sensitivity + Specificity – 1) was calculated for all steps in the risk score. Cross-tabulation was used to calculate sensitivity, specificity, and positive and negative predictive values as well as to identify the number of correctly predicted patients.

Statistical analyses were performed using IBM SPSS Statistics version 27.

External validation of the risk score

To check the predictive ability of the risk score, as well as its precision and usefulness in other populations, we performed an external validation using data from the Medication Reviews Bridging Healthcare (MedBridge) trial (25).

Study sample and procedure

The MedBridge trial (25, 26) was a randomised clinical trial conducted at four hospitals (Uppsala, Gävle, Västerås, and Enköping) in the mid-eastern part of Sweden. The aim of the trial was to study the effects of hospital-based medication reviews including post-discharge follow-up on the use of healthcare resources in older adults (≥65 years), compared with hospital-based reviews and usual care only.

Included participants were admitted to a medical ward at one of the four included hospitals for at least 24 hours within the time-frame 6th of February 2017 to the 19th of October 2018. Out of the 2637 patients included in the trial, 1745 were included in one of the two medication review groups, and 892 patients were included in the usual care group. Outcomes measured in the trial included

readmission to hospital within 30 days of discharge and possibly medication-related readmission as assessed with AT-HARM10 (24).

To make sure the medication review interventions in the MedBridge trial could not affect the result of the validation, the MedBridge control group, i.e. the 892 patients receiving usual care, was chosen to create the validation cohort in which the developed risk assessment tool was validated. In the validation cohort (n=892) 132 patients were readmitted within 30 days of discharge and 54 of these readmissions (40.9%) were assessed as being possibly medication-related.

Data analysis

A multiple logistic regression analysis with the variables included in the risk assessment tool was performed in the validation cohort, comparing patients with a possibly medication-related readmission (n=54) and those that did not have a possibly medication-related readmission (n=838) (i.e. those with an unlikely medication-related readmission (n=78) and those that were not readmitted within 30 days of discharge (n=760)). To estimate the quality of the model, Hosmer and Lemeshow goodness-of-fit was calculated as well as Negelkerke R^2.

The risk score was calculated for each of the individuals in the validation cohort and a new logistic regression analysis was performed with possibly medication-related readmission as the dependent variable and the risk score as the test variable. Probabilities were saved and used to plot a ROC-curve where the c-index was calculated giving an estimate of the predictive ability of the risk assessment tool in this external population.

Cross-tabulation was used at each of the steps in the risk score to calculate sensitivity, specificity, and positive and negative predictive values. Furthermore, the number of correctly predicted patients was identified.

Statistical analysis was performed using IBM SPSS Statistics version 27.

RESULTS

Development of the risk assessment tool

Variables included

The following variables were shown to be individually associated with possibly medication-related readmission and chosen to be included in the risk assessment tool: *Number of hospitalisations within the last 12 months, Living in own home with home care, Living in own home alone, Number of medications at admission, and Emergency admission*.

For the continuous variables, *Number of hospitalisations within the last 12 months* and *Number of medications at admission,* categorical variables were created based on comparisons of means between groups. The categorical variables were set as *Hospitalisations within the last 12 months ≥2* and *Number of medications at admission ≥5.* A new multiple logistic regression analysis was performed including these categorical variables creating the final model (Table 1).

Table 1. Final multiple logistic regression model from the model development dataset with possibly medication-related readmission within 30 days of discharge as the outcome variable[a]

Variable	OR	95%CI for OR	p-value
Age	1.00	0.98-1.03	0.927
Sex	1.01	0.68-1.49	0.969
Emergency admission	3.98	1.40-11.33	**0.010**
Hospitalisations in the last 12 months ≥2	1.54	1.04-2.28	**0.032**
Medications at admission ≥5	2.20	1.27-3.80	**0.005**
Living in own home with home care	1.85	1.18-2.91	**0.008**

Living in own home alone	1.57	1.04-2.37	**0.030**

Abbreviations: OR – Odds Ratio, CI – Confidence Interval

[a]Adjusted for gender and age.

Hosmer Lemeshow goodness of fit test p-value: 0.369. Nagelkerke R^2: 0.113.

Significant p-values are indicated in bold.

Developing the risk score

The odds ratios of the variables that were individually associated with possibly medication-related readmission were used for assigning points to each of the included variables. Hence, since the odds ratio for *Emergency admission* was about double the size of the other included variables, *Emergency admission* was assigned two points whereas the other variables were assigned one point each, giving a maximum score of six points. The resultant 0 to 6 point risk score, shown in Figure 1, was named the Hospitalisations, Own home, Medications, and Emergency admission (HOME) Score.

The model showed good calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R^2 of 0.118. The calculated area under the risk score ROC-curve (c-index) was 0.69 (95%CI 0.64-0.74).

FIGURE 1 – the HOME Score

Youden's index was calculated for each step in the risk score using the coordinates in the ROC-curve (Table 2). A suitable threshold value would be where Youden's Index is closest to 1, in this case at a score of 4 or 5.

Table 2. Youden's Index calculated for each step in the risk score in order to find a suitable threshold value

Score	Sensitivity	1-Specificity	Specificity	Youden's Index
0	1.000	1.000	0.000	0.000
1	1.000	0.974	0.026	0.026
2	0.951	0.826	0.174	0.125
3	0.937	0.795	0.205	0.142
4	0.755	0.466	0.534	0.289
5	0.413	0.169	0.831	0.244
6	0.147	0.056	0.944	0.091

A threshold score of ≥4 points was finally chosen as the threshold score. The choice was based on the desire to identify as many patients at increased risk of possibly medication-related readmission as possible, i.e. sensitivity rather than specificity should be as high as possible. At the threshold score (≥4 points) sensitivity was 76%, specificity 54%, positive predictive value 29%, and negative predictive value 90% (Table 3). The number of correctly predicted patients was 108 (out of 143).

Table 3. Diagnostic testing of the HOME Score in the development and validation cohorts

	Development cohort	Validation cohort
Sample size	720	892

Readmission within 30 days of discharge (%)	360 (50)	132 (15)
Possibly medication-related readmission (%)	143 (40)	54 (41)
Unlikely medication-related readmission (%)	217 (60)	78 (59)
Area under ROC-curve (standard error)	0.69 (0.02)	0.65 (0.04)
95% confidence interval	0.64-0.74	0.57-0.72
At HOME Score ≥ 4:		
Sensitivity, %	76	63
Specificity, %	54	51
Positive predictive value, %	29	8
Negative predictive value, %	90	96
Number of correctly predicted patients	108	34
At HOME Score ≥ 5		
Sensitivity, %	41	43
Specificity, %	83	80
Positive predictive value, %	38	12
Negative predictive value, %	85	96
Number of correctly predicted patients	59	23

External validation of the risk assessment tool

In the validation cohort only the variable *Hospitalisations within the last 12 months ≥2* was shown to be individually associated with possibly medication-related readmission (Table 4).

Logistic regression analysis in the validation cohort, with *Possibly medication-related readmission* as the dependent variable and *HOME score* as the test variable, showed good calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R^2 of 0.051.

Table 4. Comparison[a] of variables between groups in the development and validation cohort

	Development cohort			Validation cohort		
Predictor	PMRR (n=143)	Comparison group[b] (n=577)	p-value	PMRR (n=54)	Comparison group[b] (n=838)	p-value
Hospitalisations within the last 12 months ≥ 2, %	52	36	<**0.001**	30	17	**0.018**
Living in own home, with home care, %	37	18	<**0.001**	35	24	0.058
Living in own home, alone, %	53	37	<**0.001**	54	45	0.213
Number of medications at admission ≥ 5, %	87	71	<**0.001**	91	81	0.077
Emergency admission, %	97	89	**0.002**	100	96	0.150

Abbreviations: PMRR – Possibly Medication-Related Readmission

[a]A χ2-test was used for analysis in all cases, [b]Comparison group = Patients not readmitted and patients with an unlikely medication-related readmission

Significant p-values (p<0.05) are indicated in bold.

The c-index of the HOME Score was 0.65 (CI95% 0.57-0.72, p-value < 0.001) in the validation cohort. The risk score, with the cut-off point set at ≥4 points, showed a nonsignificant difference between groups (p-value 0.051). At this threshold score (≥4) sensitivity was 63%, specificity 51%, positive predictive value 8%, and negative predictive value 96% (Table 3). The number of correctly predicted

patients was 34 (out of 54). With the cut-off point set at ≥5 points there was a significant difference between groups (p value < 0.001). Sensitivity was 43%, specificity 80%, positive predictive value 12% and negative predictive value 96%. The number of correctly predicted patients was 23 (out of 54) (Table 3).

DISCUSSION

The risk assessment tool developed in this study, the HOME Score, is the first externally validated risk assessment tool that can be used to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge. The HOME Score was discriminative of possibly medication-related readmission and showed good calibration in development as well as in external validation. It is easy to use and includes variables that are readily available in the electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in the transition of care.

Comparisons to other studies

There have not yet, to our knowledge, been any risk assessment tools developed that are directly comparable to the HOME Score. However, there are several tools that can be used to identify patients at increased risk of all-cause readmission to hospital within 30 days of discharge, such as the HOSPITAL Score (27) and the LACE Index (28). There are also a few risk assessment tools related to medication-related healthcare use after discharge, such as the PRIME tool (16) and the decision support tool developed by Olson et al (17). However, none of the above-mentioned tools solely includes factors that are known already at admission as does the HOME Score.

The PRIME tool, developed by Parekh et al (16), identifies older patients (≥65 years) at increased risk of medication-related harm requiring healthcare use within eight weeks of discharge from hospital.

The tool was derived in a multicentre, prospective cohort study in the UK. In total 818 patients discharged from five UK teaching hospitals between 2013 and 2015 were included. The PRIME tool was internally validated using bootstrapping and the c-index was 0.69 before and 0.66 after validation. Hence, compared to the PRIME tool, the HOME Score has a similar predictive ability with a c-index of 0.69 in the development cohort and 0.65 in the validation cohort.

Variables included in the model

The variables included in the HOME Score were identified in our previous studies (10, 23) where we identified risk factors of all-cause readmission, possibly medication-related readmission, and unlikely medication-related readmission within 30 days of discharge, in patients 65 years and older. We chose to solely include variables known already at admission since research suggests that the successful reduction of possibly medication-related readmission demands the implementation of actions during the hospital stay (29) as well as at discharge (12) and in transitions of care (14). In order to do this, patients at increased risk of possibly medication-related readmission need to be identified already at admission. Hence, the HOME Score has an advantage compared to previously developed tools such as the PRIME tool (16), which include factors not known until discharge.

Hospitalisations within the last 12 months ≥2

The number of previous hospitalisations is a measure of disease burden and the fact that readmitted patients are more ill does not really come as a surprise since this has been shown previously (2, 23, 28). In a Swedish study from 2022, Naseer et al (30) showed that emergency department visits in older adults are significantly associated with several variables indicating disease burden, such as number of chronic diseases, number of primary care visits, number of emergency department visits, polypharmacy, and receipt of home care.

Naseer et al (31) have also shown that prior healthcare use is associated with emergency department revisits within 30 days, in older adults. Similarly, we have identified previous healthcare

use as a risk factor of possibly medication-related readmissions within 30 days of discharge (10) which is why this factor was included in the HOME Score. Prior healthcare use has also been indicated as a risk factor for all-cause readmission (23, 27, 28) and the factor is included in the HOSPITAL Score (27) as well as in the LACE Index (28).

Living in own home with home care and/or alone

Living in your own home alone is included as a variable in the HOME Score as well as in the PRIME tool (16). Living arrangements have been previously indicated as risk factors for readmission in several studies. In 2016 Olson et al (32) identified an increased risk of readmission in older men living in their own home with only their adult children as caregivers. Further, Gruneir et al (33) have shown that patients using high-risk medications have an 80% increased risk of readmission within 30 days if discharged to their own home as opposed to a nursing home. However, Naseer et al (31) did not find living alone to be explanatory of emergency department revisits in older adults. They did, on the other hand, find the receipt of home care to be significantly associated with emergency department revisits in one of the two Swedish regions studied. Similarly, Dahlberg et al (34) have shown that living at home with home care is significantly associated with unplanned (emergency) admission to hospital.

When it comes to readmission to hospital, we have previously shown that living in the community with home care is a risk factor for all-cause readmission (23) and in this study further analyses showed that it is also associated with possibly medication-related readmission. This factor is not, to our knowledge, found in other assessment tools aiming to identify all-cause readmission or possibly medication-related readmission. However, it is part of several comprehensive geriatric assessment tools aiming to identify vulnerability and frailty (35-37). Such comprehensive geriatric assessment tools have also been shown to be predictive of all-cause readmission to hospital within 30 days (35) and 60 days (36) of discharge, in older adults.

Number of medications at admission ≥5

Polypharmacy is a commonly indicated risk factor for medication-related problems in older adults (38). Polypharmacy, in itself, is not necessarily a bad thing but with age comes bodily changes that affect the pharmacokinetics and pharmacodynamics of medications. This leads to increased sensitivity (38, 39) which, in turn, leads to an increased risk of medication-related problems (38). The presence of polypharmacy (31, 40, 41) and medication-related problems (8, 42) can lead to increased healthcare use and, as shown in this study, to possibly medication-related readmissions. Hence, polypharmacy was included in the HOME Score. Similarly, the number of medications used is included as a risk factor in the PRIME tool (16) as well as in the decision support tool predicting elderly patients' risk of readmission based on their high-risk medication regimens, developed by Olson et al (17).

Emergency admission

Emergency admission, as opposed to planned admission, has been indicated as a risk factor for 30-day readmission in several studies, including ours (10, 23), and the factor is included in both the HOSPITAL Score (27) and the LACE Index (28).

In the study by Dahlberg et al (34) the only social factor significantly associated with unplanned hospital admission was living at home with home care. Furthermore, in our previous study, we showed that older adults with a possibly medication-related readmission who lived alone were more often readmitted due to an unsustainable home situation than those living with someone (10). Since living with home care and living alone are also indicated as risk factors for all-cause and possibly medication-related readmissions, this indicates that these readmitted older adults need closer supervision after discharge. At the very least they need better planning before discharge. To achieve this, the collaboration between hospital, primary, and municipal care needs to improve (12, 14).

Implications for clinical use

The HOME Score can support healthcare personnel in identifying patients at increased risk of possibly medication-related readmission. The data needed is easily attainable already at admission to hospital, thus making it possible to implement inter- and transdisciplinary activities aiming to improve medication use and transitions of care during the hospital stay as well as at discharge and in follow-up. The use of the HOME Score could likely help increase the efficiency and effectiveness of such interventions. This, in turn, could lead to an increase in patient safety as well as benefits to the health economy. Further studies are needed to test these hypotheses.

Strengths and limitations

The HOME Score was developed using data from a retrospective study performed in a population admitted to a single Swedish hospital. This could limit its generalisability, which is why an external validation was carried out using data from four other hospitals in another part of Sweden. The tool's predictive ability was withstanding, suggesting that it can be used when aiming to identify patients at increased risk of possibly medication-related readmission in Sweden. However, further studies are needed to assess the international validity of the HOME Score.

The population used in developing the HOME Score was tailored for the identification of risk factors of all-cause readmission and possibly medication-related readmission (10, 23). This led to a larger proportion of readmitted patients in the development cohort (50%) compared to the proportion in the validation cohort (15%), the proportion of 30-day readmissions in the validation cohort being closer to that reported in previous studies (1-3). This could be considered a weakness.

The tool AT-HARM10 (24) was used by clinical pharmacists in both the development (10) and validation cohort (25, 26) in order to assess whether 30-day readmissions were possibly or unlikely medication-related. Even though the tool has been validated, the assessments are implicit, and the

result depends on the person conducting them. This could be considered a weakness. However, the fact that the amount of possibly medication-related readmissions was almost the same in the development and validation cohort (40% in the development cohort and 41% in the validation cohort) indicates that this may not be a big issue.

In the development cohort, included patients were admitted to medical as well as surgical departments whereas patients in the validation cohort were admitted solely to medical wards. This could have affected the results and further validations of the HOME Score are needed in order to establish its clinical usefulness in different departments as well as in other countries.

CONCLUSION

The HOME Score can be used to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. The tool is easy to use and includes variables that are readily available in electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in transitions of care. These activities could likely help increase patient safety as well as be beneficial to the health economy. Further studies are needed to test these hypotheses.

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STATEMENTS

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors have contributed to the design of this study. MG collected, interpreted, and analysed the data with the support of the other authors. The first draft of the manuscript was completed by MG after which it was critically read and commented on by the other authors. All authors have read and approved the final manuscript.

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Ethics statement

Ethical approval was applied for and approved by the Swedish Ethics Review Authority (Dnr 2021-06612-01).

Data Availability Statement

In accordance with the Public Access to Information and Secrecy Act (43) Swedish Authorities restrict public access to the datasets analysed during the current study. However, data can be made available for research after a special review including approval of the research project by an ethics committee as well as the authorities' data safety committees. Queries regarding data access are referred to the corresponding author.

FIGURE LEGEND

Figure 1: The HOME Score to be used at admission to hospital in order to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. Hospitalisations within the last 12 months and living in own home, alone and/or with home care, refer to events and conditions prior to the admission in question.

SUPPORTING INFORMATION

Appendix 1. Assessment Tool for identifying Hospital Admissions Related to Medicine (AT-HARM10). Includes the AT-HARM10 assessment tool, instructions for use and representative examples of when a question should be answered "Yes" or "No".

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The HOME Score

Clinical risk score for predicting possibly medication-related readmission within 30 days of discharge - in patients 65 years and older

		Points
Hospitalisations	Hospitalisations within the last 12 months ≥ 2	1
Own home	Living in own home, with home care	1
	Living in own home, alone	1
Medications	Number of medications at admission ≥ 5	1
Emergency admission	Emergency admission (as opposed to planned)	2
	Total	
	A score of 4 or more denotes increased risk	

AT-HARM10 – Instructions

Assessment Tool for identifying Hospital Admissions Related to Medications

The Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10) is a screening tool consisting of 10 questions used to determine whether a hospital admission is medication-related. A medication-related admission (MRA) is a hospital admission in which a medication related problem (MRP) is either the main cause for admission or a significantly contributing cause for admission (i.e. without the MRP, the patient would not have been admitted). MRPs are defined here as "undesirable patient experiences that involve medication therapy and that actually or potentially interfere with desired patient outcomes". These not only involve adverse drug reactions to prescribed medication, but can also involve problems such as inappropriate prescribing and non-compliance, and problems related to over-the-counter (OTC) medications. It does not consider whether the admission was preventable (e.g. an admission caused by side effects of appropriate medication treatment is considered medication-related). AT-HARM10 was developed to measure the incidence of possibly medication-related admissions, MRAs.

The user of AT-HARM10 should not have to go through all patient data in the patient's medical record, because that would take too much time. The patient data from the medical records that will be provided for the assessment includes: admission notes from the current admission, medication list, laboratory data, pharmacists' notes and the discharge summary for the admission. All registered medications, including over-the-counter (OTC) medication, should be considered in the assessment. Non-registered complementary and alternative medicine (CAM) products and dietary supplements are not to be considered.

The tool comprises 10 questions which can only be answered "Yes" or "No". For further clarification of each question, please see the examples below. Questions 1-3 are used to identify admissions that are unlikely to be medication-related (U), while questions 4-10 are used to identify possibly medication-related (P) admissions. The assessment is finished as soon as the answer "Yes" is given for any question, resulting in the admission being either U or P. This means that it is not necessary to answer the remaining questions when a "Yes" answer has been given. If all the questions are answered "No", the assessment is still indecisive and needs to be examined by an expert panel.

Please note: While the reason for visiting the emergency department (ED) might be non-medication-related (e.g. chest pain, head ache), in some cases the primary cause for admission might turn out to be medication-related (e.g. low potassium levels discovered while at the ED – worsened by a diuretic). In these cases, the admission should be classified as P.

AT-HARM10

Assessment Tool for identifying Hospital Admissions Related to Medications

Note: Questions 1-3 are used to identify admissions unlikely to be medication-related, while questions 4-10 are used to identify possibly medication-related admissions. The assessment is finished as soon as the answer "Yes" is given for any question → U (unlikely to be medication-related) or P (possibly medication-related). If all the questions are answered with "No", the admission should be classified as P (possibly medication-related).

1. Was the admission caused by an *infection* or a previously *undiagnosed* disease (e.g. diabetes or heart failure) that is *not medication-related*?
   Yes → U (unlikely to be medication-related)
   No → NQ (next question)

2. Was the admission caused by progression of a previously diagnosed disease that is *not medication-related* (with the progression of several chronic diseases, such as congestive heart failure or diabetes, a medication-related component can rarely be excluded)?
   Yes → U
   No → NQ
   NOTE: Appropriateness of medication treatment should only be considered in relation to this question to determine whether the admission is primarily caused by disease progression (*unlikely* MRA) or suboptimal medication treatment or use (*possible* MRA, question 4-10).

3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies (e.g. car accident, wasp allergy, alcohol excess, mushroom poisoning) that are *not medication-related*?
   Yes → U
   No → NQ

---

4. Is it hinted or stated in the medical record that the admission was *medication-related* (including non-compliance)?
   Yes → P (possibly medication-related)
   No → NQ

5. Might (side) effects of the medications the patient was taking (prescribed or non-prescribed) prior to hospitalisation have caused the admission (including over-treatment)?
   Yes → P
   No →NQ
   NOTE: An admission caused by side effects of appropriate medication treatment should be classified as *possibly* medication-related.

6. Are there abnormal laboratory results or vital signs that could be *medication-related* and might have caused the admission?
   Yes → P
   No → NQ

7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?
   Yes → P
   No → NQ

8. Did the patient have any *previously* diagnosed untreated or suboptimally treated (e.g. dose too low) indications that might have caused the admission?
   Yes → P
   No → NQ

9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
   Yes → P
   No → NQ

10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?
    Yes → P
    No → P (the tool has not been able to rule out that the admission is medication-related)

AT-HARM10 – Examples

Assessment Tool for identifying Hospital Admissions Related to Medications

Representative examples of when a question should be answered "Yes" or "No".

1. Was the admission caused by an *infection* or a previously *undiagnosed* disease (e.g. diabetes or heart failure) that is *not medication-related*?

   Yes: A patient admitted because of pneumonia that was *not related* to the patient's *medications*.

   Yes: A patient admitted because of rectal bleeding found, after investigation, to have been caused by a tumour.

   Yes: A patient admitted with an unclear diagnosis and new symptoms. The symptoms cannot be explained by the patient's current medications.

   No: A patient receiving immunosuppressive treatment admitted with infection.

   No: A patient admitted with new symptoms indicating heart failure (oedema, shortness of breath) and a history of excessive use of non-steroidal anti-inflammatory drugs (NSAIDs).

2. Was the admission caused by progression of a previously diagnosed disease that is *not medication-related*?

   NOTE: Appropriateness of medication treatment should only be considered in relation to this question to determine whether the admission is primarily caused by disease progression (*unlikely* MRA) or suboptimal medication treatment or use (*possible* MRA, question 4-10).

   Yes: A patient admitted because of progression of cancer that is not related to the patient's medications.

   Yes: A patient admitted because of exacerbation of congestive heart-failure, which worsened despite optimal treatment (the medication therapy seems to follow the applicable treatment guidelines) and with no signs of non-compliance.

   No: A diabetic patient admitted because of hyperglycaemia without other reason for admission (hyperglycaemia should never lead to admission in a patient that is optimally treated).

3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies (e.g. car accident, wasp allergy, alcohol excess, mushroom poisoning) that are *not medication-related*?

   Yes: A patient admitted because of alcohol intoxication or a car accident that was *not related* to the use of the patient's *medications*.

   No: A patient admitted because of alcohol intoxication worsened by the concomitant use of sedatives.

4. Is it hinted or stated in the medical record that the admission is *medication-related* (including non-compliance)?

   Yes: A physician states in the discharge note that the patient was admitted because of constipation caused by the lack of laxative therapy during treatment with a strong opioid.

   Yes: A patient admitted because of an epileptic seizure and a note in the medical records that the patient is known to be non-compliant.

5. Might (side) effects of the medications the patient was taking (prescribed or non-prescribed) prior to hospitalisation have caused the admission (including over-treatment)?

   NOTE: An admission caused by side effects of appropriate medication treatment should be classified as *possibly* medication-related.

   Yes: A patient admitted with gastric bleeding who uses acetylsalicylic acid to prevent thrombotic events (regardless of the presence of a correct indication and the use of a proton pump inhibitor for gastric protection).

   Yes: A patient admitted because of lactic acidosis after continuing medication with metformin while experiencing dehydrating stomach flu.

   Yes: A patient who uses antihypertensive medication and was admitted due to a fall caused by orthostatic hypotension.

6. Are there abnormal laboratory results or vital signs that could be *medication-related* and might have caused the admission?

   Yes: A patient admitted with a serum digoxin concentration of 3.4 nmol/L (toxic concentration) which may have been the cause for admission.

   Yes: A patient admitted because of hypokalaemia (s-potassium < 3.5 mmol/L) and prescribed a diuretic.

   Yes: A patient with epilepsy admitted with seizures and prescribed a seemingly adequate dose of carbamazepine but with a measured plasma concentration that is too low.

7. Was there any *drug-drug interaction* or *drug-disease interaction* (i.e. a contraindication) that might have caused the admission?

   Yes: A patient admitted because of gastrointestinal bleeding who was taking diclofenac and warfarin in combination before admission.

   Yes: A patient admitted because of serotonin syndrome who was taking tramadol, citalopram and mirtazapine.

Yes: A patient, previously diagnosed with bilateral renal artery stenosis, admitted because of acute renal failure after taking an ACE inhibitor.

Yes: A patient with dementia, who has recently been prescribed an anticholinergic medication (e.g. hydroxyzine), admitted with confusion.

8. Did the patient have any, *previously* diagnosed, untreated or suboptimally treated (e.g. dose too low) indications that might have caused the admission?

   Yes: A patient diagnosed with congestive heart failure, who was taking only a starting dose of ACE-inhibitor (unjustifiably low dose), admitted because of fluid retention and dyspnoea.

   Yes: A patient admitted because of a hip fracture who had a prior diagnosis of osteoporosis but was not taking osteoporosis prophylaxis.

9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?

   Yes: A patient admitted with worsening asthma who was found to be unable to use the inhalers correctly.

   Yes: A patient admitted with palpitations who was found to be unable to swallow tablets and had been crushing slow-release antihypertensive tablets that should have been swallowed whole to retain their slow-release effects.

10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?

    Yes: A patient whose prednisolone treatment has been discontinued too abruptly admitted with nausea, vomiting and diarrhoea.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5-6, 7-8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5, 7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5, 7
	5b	D;V	Describe eligibility criteria for participants.	5, 7
	5c	D;V	Give details of treatments received, if relevant.	-
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	Prev study
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Prev study
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6-7
	10c	V	For validation, describe how the predictions were calculated.	8
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6-7,8
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	7
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11-12
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Prev studies
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	13
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	11-12
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	-
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	D	Explain how to the use the prediction model.	10, Fig 1
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	9, 10, 13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	-
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	18-19
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14,18
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14-17
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-18
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	19

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Identifying older adults at increased risk of medication-related readmission to hospital within 30 days of discharge - development and validation of a risk assessment tool

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Identifying older adults at increased risk of medication-related readmission to hospital within 30 days of discharge - development and validation of a risk assessment tool

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ABSTRACT

Objective

Developing and validating a risk assessment tool aiming to identify older adults (≥ 65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge.

Design

Retrospective cohort study.

Setting

The risk score was developed using data from a hospital in southern Sweden and validated using data from four hospitals in the mid-eastern part of Sweden.

Participants

The development cohort (n=720) was admitted to hospital during 2017 whereas the validation cohort (n=892) was admitted during 2017-2018.

Measures

The risk assessment tool aims to predict possibly medication-related readmission to hospital within 30 days of discharge. Variables known at first admission and individually associated with possibly medication-related readmission were used in development. The included variables were assigned points and Youden's index was used to decide a threshold score. The risk score was calculated for all individuals in both cohorts. Area under the ROC-curve (c-index) was used to measure the discrimination of the developed risk score. Sensitivity, specificity, and positive and negative predictive values were calculated using cross-tabulation.

Results

The developed risk assessment tool, the HOME Score, had a c-index of 0.69 in the development cohort and 0.65 in the validation cohort. It showed sensitivity 76%, specificity 54%, positive predictive value 29%, and negative predictive value 90% at the threshold score in the development cohort.

Conclusion

The HOME Score can be used to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. The tool is easy to use and includes variables available in electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in transitions of care. Further studies are needed to investigate the clinical usefulness of the HOME Score as well as the benefits of implemented activities.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- In this study a risk assessment tool - the HOME Score – aiming to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge was developed and externally validated.
- Only variables available in the electronic health records at admission to hospital were included in the risk assessment tool.
- Possibly medication-related readmissions were identified using the same tool, AT-HARM10, in both the development cohort and the validation cohort.
- Further validations of the HOME Score are needed in order to establish its clinical usefulness in different departments as well as in other countries.

INTRODUCTION

Readmission to hospital is common, especially in older adults where almost 20% of discharges result in a readmission within 30 days (1-3). In older adults, hospitalisation can be associated with a risk of complications such as exposure to infections, rise in adverse events, episodes of confusion, and accidental injury through falls (4, 5). As readmissions are not only a risk for the individual patient but also for the health economy (3), many countries have set goals to decrease the frequency of readmission within 30 days of discharge (3, 6, 7).

According to previous research (8-10) a relatively large proportion of readmissions to hospital, in older adults, is medication-related. However, the amount differs greatly between studies as shown in a systematic review by El Morabet et al (8). In this study the amount of medication-related readmission reported was 3-64% with a median of 21% (interquartile range 14-23%). These differences are due to a number of factors, one being the use of different definitions of “medication-related” between studies (8). While some studies measure readmissions related to adverse drug

reactions, adverse drug events, or drug-drug reactions others measure readmissions related to medication-related problems, thus including all the above-mentioned problems (8).

Many medication-related readmissions may be possible to prevent, even though the proportion deemed preventable also differs between studies (8), again, due to differences in methods used. According to previous research, preventive measures should aim to improve medication use as well as transitions of care (11, 12) and are best performed by combining several minor activities into concepts (12, 13). These activities should preferably include interdisciplinary actions during the hospital stay and at discharge (12) as well as collaboration between hospital, primary, and municipal care in transitions of care (14).

To effectively implement interventions, healthcare personnel need to be able to identify patients at increased risk of medication-related readmission. This could preferably be done by using a risk assessment tool or risk score (15). Some risk assessment tools linked to medication-related readmission have been developed (16, 17). The PRIME tool, developed by Parekh et al (16), identifies older adults at increased risk of medication-related harm requiring healthcare use within eight weeks of discharge while the decision support tool developed by Olson et al (17) predicts the risk of readmission in older adults using high-risk medication regimens. None of these tools have been validated in an external population or tested in a setting other than the one where it was developed.

To our knowledge, there is no risk assessment tool available that specifically aims to identify older adults at increased risk of possibly medication-related readmission to hospital within 30 days of discharge. If such a tool was available, interventions aiming to prevent readmission could be implemented based on the risk in the individual patient (15). This could make it possible to not only increase patient safety but also relocate some resources to other areas within healthcare.

OBJECTIVE

The aim of this study was to develop and validate a risk assessment tool that can be used to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge.

METHODS

This study is reported according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement (15).

Setting

Sweden is divided into 21 regions and 290 municipalities (18). Primary and hospital care is provided by the regions while nursing care, in the community or in nursing homes, is provided by the local municipalities. When it comes to planning patient care after hospital discharge, hospital and municipal care are expected to collaborate (19).

According to Swedish directives and general advice (20), a medication reconciliation should be performed by the attending physician when patients aged 75 years and older using five medications or more are admitted to hospital. In performing the medication reconciliation, the attending physician can be supported by other healthcare personnel, e.g. a clinical pharmacist.

If medication-related problems are present, the medication reconciliation should be followed by a medication review which could or could not be performed interdisciplinary (i.e. involving a geriatrician or a clinical pharmacist). Unfortunately, adherence to these directives seems generally low (21) with only about 15% of patients aged 75 years and older receiving a medication reconciliation and/or medication review during their hospital stay (21).

Patient and public involvement

Patients or the public were not involved in this study.

Development of the risk assessment tool

The risk assessment tool was developed using anonymised data and results from our previously published retrospective studies (10, 22) where further details on the population and methods of data collection can be found.

Study sample and procedure

The study was conducted at Kristianstad hospital, which is an emergency hospital with 255 beds situated in Skåne county in the south of Sweden. The study population, which is further referred to as the development cohort, consisted of randomly selected patients (n=720), aged 65 years and older, who had been admitted to Kristianstad hospital for at least 24 hours in 2017. Patients were admitted to one of the following departments: internal medicine, infectious disease, general surgery, orthopaedics, or ear/nose/throat. The study group (n=360) was readmitted to any department in the hospital, for at least 24 hours, within 30 days of discharge while the comparison group (n=360) was not. Variables were collected from electronic health records in an unblinded yet standardised and objective manner, as previously described (22).

In total 143 of 360 readmissions (39.7%) were assessed as being possibly medication-related (10). Assessments were made using the Assessment Tool for identifying Hospital Admissions Related to Medication (AT-HARM10), a validated tool to distinguish between admissions that are possibly and unlikely medication-related (23). With AT-HARM10 a possibly medication-related (re-)admission is defined as being either caused by or significantly contributed to by a medication-related problem and a medication-related problem is defined according to Strand (24), i.e. as an "undesirable patient experience that involves medication therapy and that actually or potentially

interferes with desired patient outcomes" (23). This means that medication-related problems involve not only adverse drug reactions or adverse drug events but also problems such as inappropriate prescribing, non-compliance, and problems related to over-the-counter medications (23). For further details on AT-HARM10, see Appendix 1.

Preliminary assessments, made by the first author in an unblinded fashion, were reviewed, revised, and finalised by an experienced geriatrician. For further details on the assessment process see our previous publication (10).

Through multiple logistic regression analysis (stepwise backward) individual risk factors associated with all-cause readmission, possibly medication-related readmission, and unlikely medication-related readmission within 30 days of discharge were identified, as described in our previous publications (10, 22).

Variables included

The risk assessment tool was developed using variables identified by comparing patients with a possibly medication-related readmission (n=143) with those that did not have a possibly medication-related readmission (n=577) (i.e. patients with an unlikely medication-related readmission (n=217) and patients not readmitted (n=360)). Only variables known at first admission to hospital were included in the development of the risk assessment tool.

Variables shown to be associated with possibly medication-related readmission, through multiple logistic regression analysis, were chosen to be included in the final risk assessment tool. For continuous variables, categorical variables were created based on comparisons between groups.

Data analysis

Based on the odds ratios of the individual variables in the final multiple logistic regression model, suitable weighting and scoring were decided upon for each of the included variables. A risk score,

which summarised the points assigned to each of the variables included, was calculated for all the included individuals. Finally, a new logistic regression analysis was performed with possibly medication-related readmission as the dependent variable and the risk score as the test variable, saving the probabilities for further analysis. To estimate the quality of the model Hosmer and Lemeshow goodness-of-fit was calculated as well as Nagelkerke R^2.

A ROC-curve was plotted using the saved probabilities and the area under the ROC-curve (c-index) was calculated giving a measure of how well the tool predicts possibly medication-related readmission.

To decide upon a suitable threshold value in the risk assessment tool Youdens' index (J = Sensitivity + Specificity – 1) was calculated for all steps in the risk score. Cross-tabulation was used to calculate sensitivity, specificity, and positive and negative predictive values as well as to identify the number of correctly predicted patients.

Statistical analyses were performed using IBM SPSS Statistics version 27.

External validation of the risk score

To check the predictive ability of the risk score, as well as its precision and usefulness in other populations, we performed an external validation using data from the Medication Reviews Bridging Healthcare (MedBridge) trial (25, 26).

Study sample and procedure

The MedBridge trial (25, 26) was a randomised clinical trial conducted at four hospitals (Uppsala, Gävle, Västerås, and Enköping) in the mid-eastern part of Sweden. The aim of the trial was to study the effects of hospital-based medication reviews including post-discharge follow-up on the use of healthcare resources in older adults (≥65 years), compared with hospital-based reviews and usual care only.

Included participants were admitted to a medical ward at one of the four included hospitals for at least 24 hours within the time-frame 6th of February 2017 to the 19th of October 2018. Out of the 2637 patients included in the trial, 1745 were included in one of the two medication review groups, and 892 patients were included in the group receiving usual care. Outcomes measured in the trial included readmission to hospital within 30 days of discharge and possibly medication-related readmission as assessed with AT-HARM10 (24). For further details on the population and methods of data collection used in the MedBridge trial, see Kempen et al (25).

To make sure the medication review interventions in the MedBridge trial could not affect the result of the validation, the MedBridge control group, i.e. the 892 patients receiving usual care, was chosen to create the validation cohort in which the developed risk assessment tool was validated. In the validation cohort (n=892) 132 patients were readmitted within 30 days of discharge and 54 of these readmissions (40.9%) were assessed as being possibly medication-related.

Data analysis

A multiple logistic regression analysis with the variables included in the risk assessment tool was performed in the validation cohort, comparing patients with a possibly medication-related readmission (n=54) and those that did not have a possibly medication-related readmission (n=838) (i.e. those with an unlikely medication-related readmission (n=78) and those that were not readmitted within 30 days of discharge (n=760)). To estimate the quality of the model, Hosmer and Lemeshow goodness-of-fit was calculated as well as Nagelkerke R^2.

The risk score was calculated for each of the individuals in the validation cohort and a new logistic regression analysis was performed with possibly medication-related readmission as the dependent variable and the risk score as the test variable. Probabilities were saved and used to plot a ROC-curve where the c-index was calculated giving an estimate of the predictive ability of the risk assessment tool in this external population.

Cross-tabulation was used at each of the steps in the risk score to calculate sensitivity, specificity, and positive and negative predictive values. Furthermore, the number of correctly predicted patients was identified.

Statistical analysis was performed using IBM SPSS Statistics version 27.

RESULTS

Development of the risk assessment tool

Variables included

The following variables were shown to be individually associated with possibly medication-related readmission and chosen to be included in the risk assessment tool: *Number of hospitalisations within the last 12 months, Living in own home with home care, Living in own home alone, Number of medications at admission, and Emergency admission*.

For the continuous variables, *Number of hospitalisations within the last 12 months* and *Number of medications at admission,* categorical variables were created based on comparisons of means and medians between groups.

The mean number of hospitalisations in patients with a possibly medication-related readmission was 1.94 and the median was 2. The mean number in the comparison group (including patients not readmitted and those with a readmission unlikely related to medications) was 1.67 and the median was 1. Hence, the categorical variable was set as *Hospitalisations within the last 12 months ≥2*.

The mean number of medications at first admission to hospital in patients with a possibly medication-related readmission and in the comparison group (i.e. patients not readmitted and those with a readmission unlikely related to medications) was 10.30 and 8.09 respectively, and the median

was 10 and 7 respectively. Both the categorical variable *Number of medications at admission ≥5* and *Number of medications at admission ≥10* were tested in the multiple logistic regression model. Both variables showed similar odds ratios (2.20 with number of medications ≥5 and 1.99 with number of medications ≥10) and both had significant p-values (0.005 with number of medications ≥5 and <0.001 with number of medications ≥10). Finally, we chose to use the categorical variable *Number of medications at admission ≥5* in the final model (Table 1).

Table 1. Final multiple logistic regression model from the model development dataset with possibly medication-related readmission within 30 days of discharge as the outcome variable[a]

Variable	OR	95%CI for OR	p-value
Age	1.00	0.98-1.03	0.986
Sex	1.02	0.69-1.50	0.939
Emergency admission	4.03	1.42-11.45	**0.009**
Hospitalisations in the last 12 months ≥2	1.53	1.04-2.27	**0.033**
Medications at admission ≥5	2.20	1.27-3.80	**0.005**
Living in own home with home care	1.84	1.17-2.89	**0.009**
Living in own home alone	1.59	1.06-2.39	**0.026**

Abbreviations: OR – Odds Ratio, CI – Confidence Interval

[a]*Adjusted for gender and age.*

Hosmer Lemeshow goodness of fit test p-value: 0.802. Nagelkerke R^2: 0.113.

Significant p-values are indicated in bold.

Developing the risk score

The odds ratios of the variables that were individually associated with possibly medication-related readmission were used for assigning points to each of the included variables. Hence, since the odds ratio for *Emergency admission* was about double the size of the other included variables, *Emergency admission* was assigned two points whereas the other variables were assigned one point each, giving a maximum score of six points. The resultant 0 to 6 point risk score, shown in Figure 1, was named the Hospitalisations, Own home, Medications, and Emergency admission (HOME) Score.

The model showed fair calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R^2 of 0.117. The calculated area under the risk score ROC-curve (c-index) was 0.69 (95%CI 0.64-0.74).

FIGURE 1 – the HOME Score

Youden's index was calculated for each step in the risk score using the coordinates in the ROC-curve (Table 2). A suitable threshold value would be where Youden's Index is closest to 1, in this case at a score of 4 or 5.

Table 2. Youden's Index calculated for each step in the risk score in order to find a suitable threshold value

Score	Sensitivity	1-Specificity	Specificity	Youden's Index

0	1.000	1.000	0.000	0.000
1	1.000	0.974	0.026	0.026
2	0.951	0.827	0.173	0.124
3	0.937	0.794	0.206	0.143
4	0.755	0.466	0.534	0.289
5	0.413	0.170	0.830	0.243
6	0.147	0.055	0.945	0.092

A threshold score of ≥4 points was finally chosen as the threshold score. The choice was based on the desire to identify as many patients at increased risk of possibly medication-related readmission as possible, i.e. sensitivity rather than specificity should be as high as possible. At the threshold score (≥4 points) sensitivity was 76%, specificity 53%, positive predictive value 29%, and negative predictive value 90% (Table 3). The number of correctly predicted patients was 108 (out of 143).

Table 3. Diagnostic testing of the HOME Score in the development and validation cohorts

	Development cohort	Validation cohort
Sample size	720	892
Readmission within 30 days of discharge, n (%)	360 (50)	132 (15)
Possibly medication-related readmission, n (%)	143 (40)	54 (41)
Unlikely medication-related readmission, n (%)	217 (60)	78 (59)
Area under ROC-curve (standard error)	0.69 (0.02)	0.65 (0.04)
95% confidence interval	0.64-0.74	0.57-0.72
Patient distribution		

HOME Score <4, n (%)	343 (48)	443 (50)
HOME Score ≥ 4, n (%)	377 (52)	447 (50)
Patients with possibly medication-related readmission		
HOME Score <4, n (%)	35 (10)	20 (5)
HOME Score ≥ 4, n (%)	108 (29)	34 (8)
At HOME Score ≥ 4:		
Sensitivity, %	76	63
Specificity, %	53	51
Positive predictive value, %	29	8
Negative predictive value, %	90	96
Number of correctly predicted patients, n	108	34
At HOME Score ≥ 5		
Sensitivity, %	41	43
Specificity, %	83	80
Positive predictive value, %	38	12
Negative predictive value, %	85	96
Number of correctly predicted patients, n	59	23

External validation of the risk assessment tool

In the validation cohort only the variable *Hospitalisations within the last 12 months ≥2* was shown to be individually associated with possibly medication-related readmission (Table 4).

Logistic regression analysis in the validation cohort, with *Possibly medication-related readmission* as the dependent variable and *HOME score* as the test variable, showed fair calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R^2 of 0.051.

Table 4. Comparison[a] of variables between groups in the development and validation cohort

	Development cohort			Validation cohort		
Predictor	PMRR (n=143)	Comparison group[b] (n=577)	p-value	PMRR (n=54)	Comparison group[b] (n=838)	p-value
Hospitalisations within the last 12 months ≥ 2, %	52	36	<**0.001**	30	17	**0.018**
Living in own home, with home care, %	37	18	<**0.001**	35	24	0.058
Living in own home, alone, %	53	37	<**0.001**	54	45	0.213
Number of medications at admission ≥ 5, %	87	71	<**0.001**	91	81	0.077
Emergency admission, %	97	89	**0.002**	100	96	0.150

Abbreviations: PMRR – Possibly Medication-Related Readmission

[a]A χ2-test was used for analysis in all cases, [b]Comparison group = Patients not readmitted and patients with an unlikely medication-related readmission

Significant p-values (p<0.05) are indicated in bold.

The c-index of the HOME Score was 0.65 (CI95% 0.57-0.72, p-value < 0.001) in the validation cohort. The risk score, with the cut-off point set at ≥4 points, showed a nonsignificant difference between groups (p-value 0.051). At this threshold score (≥4) sensitivity was 63%, specificity 51%, positive predictive value 8%, and negative predictive value 96% (Table 3). The number of correctly predicted

patients was 34 (out of 54). With the cut-off point set at ≥5 points there was a significant difference between groups (p value < 0.001). Sensitivity was 43%, specificity 80%, positive predictive value 12% and negative predictive value 96%. The number of correctly predicted patients was 23 (out of 54) (Table 3).

DISCUSSION

The risk assessment tool developed in this study, the HOME Score, is the first externally validated risk assessment tool that can be used to identify older adults (≥65 years) at increased risk of possibly medication-related readmission to hospital within 30 days of discharge. The HOME Score was fairly discriminative of possibly medication-related readmission and showed fair calibration in development as well as in external validation. The tool is easy to use and includes variables that should be readily available in the electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in transitions of care.

Comparisons to other studies

There have not yet, to our knowledge, been any risk assessment tools developed that are directly comparable to the HOME Score. However, there are several tools that can be used to identify patients at increased risk of all-cause readmission to hospital within 30 days of discharge, such as the HOSPITAL Score (27), the LACE Index (28), and the PAR-Risk Score (29). Even though the PAR-Risk Score focuses on medications as a risk factor for potentially avoidable hospital readmissions, it does not specifically predict medication-related readmissions. There are, however, a few risk assessment tools related to medication-related healthcare use after discharge, such as the PRIME tool (16) and

the decision support tool developed by Olson et al (17). None of the above-mentioned tools solely includes factors that are known already at admission as does the HOME Score.

The PRIME tool, developed by Parekh et al (16), identifies older patients (≥65 years) at increased risk of medication-related harm requiring healthcare use within eight weeks of discharge from hospital. The tool was derived in a multicentre, prospective cohort study in the UK. In total 818 patients discharged from five UK teaching hospitals between 2013 and 2015 were included. The PRIME tool was internally validated using bootstrapping and the c-index was 0.69 before and 0.66 after validation. Hence, compared to the PRIME tool, the HOME Score has a similar predictive ability with a c-index of 0.69 in the development cohort and 0.65 in the validation cohort.

With the PRIME tool (16) healthcare use after discharge includes not only hospital readmissions but also other healthcare use such as visits to the emergency department, in-person or telephone consultations with a general practitioner, or visits to outpatient clinics. This means that the PRIME tool predicts healthcare use in broader sense than does the HOME Score. Further, medication-related harm in the PRIME tool is defined as adverse drug reactions and harm arising from non-adherence only while the HOME Score defines medication-related problems more broadly, also including problems such as inappropriate prescribing and problems related to over-the-counter medications (see Appendix 1) (23).

Variables included in the model

The variables included in the HOME Score were identified in our previous studies (10, 22) where we identified risk factors for all-cause readmission, possibly medication-related readmission, and unlikely medication-related readmission within 30 days of discharge, in patients 65 years and older. We chose to solely include variables known already at admission since research suggests that the successful reduction of possibly medication-related readmission demands the implementation of actions during the hospital stay (30) as well as at discharge (12) and in transitions of care (14). In order to do this, patients at increased risk of possibly medication-related readmission need to be

identified already at admission. Hence, the HOME Score has an advantage compared to previously developed tools such as the PRIME tool (16), which include factors not known until discharge.

Hospitalisations within the last 12 months ≥2

The number of previous hospitalisations is a measure of disease burden and the fact that readmitted patients are more ill does not really come as a surprise since this has been shown previously (2, 22, 28). In a Swedish study from 2022, Naseer et al (31) showed that emergency department visits in older adults are significantly associated with several variables indicating disease burden, such as number of chronic diseases, number of primary care visits, number of emergency department visits, polypharmacy, and receipt of home care.

Naseer et al (32) have also shown that prior healthcare use is associated with emergency department revisits within 30 days, in older adults. Similarly, we have identified previous healthcare use as a risk factor of possibly medication-related readmissions within 30 days of discharge (10) which is why this factor was included in the HOME Score. Prior healthcare use has also been indicated as a risk factor for all-cause readmission (22, 27, 28) and the factor is included, in some form, in the HOSPITAL Score (27), the LACE Index (28), and the PAR-Risk Score (29).

Living in own home with home care and/or alone

Living in your own home alone is included as a variable in the HOME Score as well as in the PRIME tool (16). Living arrangements have been previously indicated as risk factors for readmission in several studies. In 2016 Olson et al (33) identified an increased risk of readmission in older men living in their own home with only their adult children as caregivers. Further, Gruneir et al (34) have shown that patients using high-risk medications have an 80% increased risk of readmission within 30 days if discharged to their own home as opposed to a nursing home. However, Naseer et al (32) did not find living alone to be explanatory of emergency department revisits in older adults. They did, on the other hand, find the receipt of home care to be significantly associated with emergency

department revisits in one of the two Swedish regions studied. Similarly, Dahlberg et al (35) have shown that living at home with home care is significantly associated with unplanned (emergency) admission to hospital.

When it comes to readmission to hospital, we have previously shown that living in the community with home care is a risk factor for all-cause readmission (22) and in this study further analyses showed that it is also associated with possibly medication-related readmission. This factor is not, to our knowledge, found in other assessment tools aiming to identify all-cause readmission or possibly medication-related readmission. However, it is part of several comprehensive geriatric assessment tools aiming to identify vulnerability and frailty (36-38). Such comprehensive geriatric assessment tools have also been shown to be predictive of all-cause readmission to hospital within 30 days (36) and 60 days (37) of discharge, in older adults.

Number of medications at admission ≥5

Polypharmacy is a commonly indicated risk factor for medication-related problems in older adults (39). Polypharmacy, in itself, is not necessarily a bad thing but with age comes physiological changes that affect the pharmacokinetics and pharmacodynamics of medications. This leads to increased sensitivity (39, 40) which, in turn, leads to an increased risk of medication-related problems (39). The presence of polypharmacy (32, 41, 42) and medication-related problems (8, 43) can lead to increased healthcare use and, as shown in this study, to possibly medication-related readmissions. Hence, polypharmacy was included in the HOME Score. Similarly, the number of medications used is included as a risk factor in the PRIME tool (16) as well as in the decision support tool predicting elderly patients' risk of readmission based on their high-risk medication regimens, developed by Olson et al (17).

Emergency admission

Emergency admission, as opposed to planned admission, has been indicated as a risk factor for 30-day readmission in several studies, including ours (10, 22), and the factor is included in both the HOSPITAL Score (27) and the LACE Index (28).

In the study by Dahlberg et al (35) the only social factor significantly associated with unplanned hospital admission was living at home with home care. Furthermore, in our previous study, we showed that older adults with a possibly medication-related readmission who lived alone were more often readmitted due to an unsustainable home situation than those living with someone (10). Since living with home care and living alone are also indicated as risk factors for all-cause and possibly medication-related readmissions, this indicates that these readmitted older adults need closer supervision after discharge. At the very least they need better planning before discharge. To achieve this, the collaboration between hospital, primary, and municipal care needs to improve (12, 14).

Implications for clinical use

Healthcare involving multimorbid older adults is complex and integrating care across disciplines, as well as working together in interdisciplinary teams, is important to achieve safe and effective healthcare (11, 12, 14, 44). Improving medication use as well as transitions of care has been shown to be important factors when aiming to reduce the frequency of medication-related readmissions (11, 12). Including clinical pharmacists in the interdisciplinary team, to help with medication reconciliation and medication review as well as information transfer and follow-up regarding medications and medication changes, can support this (12, 45-47). The HOME Score can be used to find the patients in most need of this support.

Even though the positive predictive value of the HOME score is quite low (29% in the development cohort and 8% in the validation cohort), it could be useful in clinical practice, especially considering the negative predictive value. Among the 50% of older adults identified as at low risk of medication-

related readmission, 90% of patients in the development cohort and 96% in the validation cohort were indeed not readmitted due to medication-related problems. Hence, using the HOME Score, healthcare personnel can easily rule out 50% of patients 65 years and older who are not at increased risk of medication-related readmission. This can be done already at admission to hospital, and in doing so, the efficiency and effectiveness of preventive actions aiming to improve medication use and transitions of care can probably improve. This can possibly, in turn, lead to an increase in patient safety as well as benefits to the health economy. Further studies are needed to test these hypotheses.

Strengths and limitations

According to the TRIPOD statement (15) an internal validation should always be performed when developing a prediction model, which was not done in this study. This choice was based on the fact that an external validation, using a geographically separate population, was performed. We considered this to be sufficient as clinical prediction models are always in need of further validation studies, as performance differs between locations, settings, and over time (48). Hence, this is just a first edition of the HOME Score and further studies are needed to test its clinical usefulness and to keep it up-to-date.

The HOME Score was developed using data from a retrospective study performed in a population admitted to a single Swedish hospital. This could limit its generalisability, which is why an external validation was carried out using data from four other hospitals in another part of Sweden. The tool's predictive ability was withstanding, suggesting that it can be used when aiming to identify patients at increased risk of possibly medication-related readmission in Sweden. However, further studies are needed to assess the international validity of the HOME Score as well as its validity in other populations within Sweden. As stated previously, this is merely a first edition of the HOME Score and further studies are needed to test its clinical usefulness and to keep it updated.

We chose to include the categorical variable *Number of medications at admission ≥5* in the final risk score even though the mean number of medications was 10.30 in patients with a possibly medication-related readmission and 8.09 in the comparison group. This choice was based on the Swedish directives and general advice (20) stating that a medication reconciliation should be performed in admitted patients taking 5 medications or more, but it may have weakened the prediction model. This is one of the aspects that should be examined when further validating the HOME Score and investigating its clinical usefulness.

The population used in developing the HOME Score was tailored for the identification of risk factors for all-cause readmission and possibly medication-related readmission (10, 22). This led to a larger proportion of readmitted patients in the development cohort (50%) compared to the proportion in the validation cohort (15%), the proportion of 30-day readmissions in the validation cohort being closer to that reported in previous studies (1-3). This could be considered a weakness.

The tool AT-HARM10 (23) was used by clinical pharmacists in both the development (10) and validation cohort (25, 26) in order to assess whether 30-day readmissions were possibly or unlikely medication-related. This is a strength as the same definition of medication-related readmission was used in both populations. However, even though the tool has been validated (23), the assessments are implicit, and the result depends on the person conducting them. This could be considered a weakness. The fact that the amount of possibly medication-related readmissions was almost the same in the development and validation cohort (40% in the development cohort and 41% in the validation cohort) indicates that this may not be a big issue.

In the development cohort, included patients were admitted to medical as well as surgical departments whereas patients in the validation cohort were admitted solely to medical wards. This could have affected the results and further validations of the HOME Score are needed in order to establish its clinical usefulness in different departments as well as in other countries.

CONCLUSION

The HOME Score can be used to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. The tool is easy to use and includes variables that should be readily available in electronic health records at admission, thus making it possible to implement risk-reducing activities during the hospital stay as well as at discharge and in transitions of care. These activities could possibly help increase patient safety as well as be beneficial to the health economy but further studies are needed to investigate the clinical usefulness of the HOME Score as well as the benefits of implemented activities.

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STATEMENTS

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors have contributed to the design of this study. MG collected, interpreted, and analysed the data with the support of the other authors. The first draft of the manuscript was completed by MG after which it was critically read and commented on by the other authors. All authors have read and approved the final manuscript.

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Ethics statement

Ethical approval was applied for and approved by the Swedish Ethics Review Authority (Dnr 2021-06612-01).

Data Availability Statement

In accordance with the Public Access to Information and Secrecy Act (49) Swedish Authorities restrict public access to the datasets analysed during the current study. However, data can be made available for research after a special review including approval of the research project by an ethics committee as well as the authorities' data safety committees. Queries regarding data access are referred to the corresponding author.

FIGURE LEGEND

Figure 1: The HOME Score to be used at admission to hospital in order to identify older adults at increased risk of possibly medication-related readmission within 30 days of discharge. Hospitalisations within the last 12 months and living in own home, alone and/or with home care, refer to events and conditions prior to the admission in question.

SUPPORTING INFORMATION

Appendix 1. Assessment Tool for identifying Hospital Admissions Related to Medicine (AT-HARM10). Includes the AT-HARM10 assessment tool, instructions for use and representative examples of when a question should be answered "Yes" or "No".

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The HOME Score

Clinical risk score for predicting possibly medication-related readmission within 30 days of discharge - in patients 65 years and older

		Points
Hospitalisations	Hospitalisations within the last 12 months ≥ 2	1
Own home	Living in own home, with home care	1
	Living in own home, alone	1
Medications	Number of medications at admission ≥ 5	1
Emergency admission	Emergency admission (as opposed to planned)	2
	Total	
	A score of 4 or more denotes increased risk	

AT-HARM10 – Instructions

Assessment Tool for identifying Hospital Admissions Related to Medications

The Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10) is a screening tool consisting of 10 questions used to determine whether a hospital admission is medication-related. A medication-related admission (MRA) is a hospital admission in which a medication related problem (MRP) is either the main cause for admission or a significantly contributing cause for admission (i.e. without the MRP, the patient would not have been admitted). MRPs are defined here as "undesirable patient experiences that involve medication therapy and that actually or potentially interfere with desired patient outcomes". These not only involve adverse drug reactions to prescribed medication, but can also involve problems such as inappropriate prescribing and non-compliance, and problems related to over-the-counter (OTC) medications. It does not consider whether the admission was preventable (e.g. an admission caused by side effects of appropriate medication treatment is considered medication-related). AT-HARM10 was developed to measure the incidence of possibly medication-related admissions, MRAs.

The user of AT-HARM10 should not have to go through all patient data in the patient's medical record, because that would take too much time. The patient data from the medical records that will be provided for the assessment includes: admission notes from the current admission, medication list, laboratory data, pharmacists' notes and the discharge summary for the admission. All registered medications, including over-the-counter (OTC) medication, should be considered in the assessment. Non-registered complementary and alternative medicine (CAM) products and dietary supplements are not to be considered.

The tool comprises 10 questions which can only be answered "Yes" or "No". For further clarification of each question, please see the examples below. Questions 1-3 are used to identify admissions that are unlikely to be medication-related (U), while questions 4-10 are used to identify possibly medication-related (P) admissions. The assessment is finished as soon as the answer "Yes" is given for any question, resulting in the admission being either U or P. This means that it is not necessary to answer the remaining questions when a "Yes" answer has been given. If all the questions are answered "No", the assessment is still indecisive and needs to be examined by an expert panel.

Please note: While the reason for visiting the emergency department (ED) might be non-medication-related (e.g. chest pain, head ache), in some cases the primary cause for admission might turn out to be medication-related (e.g. low potassium levels discovered while at the ED – worsened by a diuretic). In these cases, the admission should be classified as P.

AT-HARM10

Assessment Tool for identifying Hospital Admissions Related to Medications

Note: Questions 1-3 are used to identify admissions unlikely to be medication-related, while questions 4-10 are used to identify possibly medication-related admissions. The assessment is finished as soon as the answer "Yes" is given for any question → U (unlikely to be medication-related) or P (possibly medication-related). If all the questions are answered with "No", the admission should be classified as P (possibly medication-related).

1. Was the admission caused by an *infection* or a previously *undiagnosed* disease (e.g. diabetes or heart failure) that is *not medication-related*?
   Yes → U (unlikely to be medication-related)
   No → NQ (next question)

2. Was the admission caused by progression of a previously diagnosed disease that is *not medication-related* (with the progression of several chronic diseases, such as congestive heart failure or diabetes, a medication-related component can rarely be excluded)?
   Yes → U
   No → NQ
   NOTE: Appropriateness of medication treatment should only be considered in relation to this question to determine whether the admission is primarily caused by disease progression (*unlikely* MRA) or suboptimal medication treatment or use (*possible* MRA, question 4-10).

3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies (e.g. car accident, wasp allergy, alcohol excess, mushroom poisoning) that are *not medication-related*?
   Yes → U
   No → NQ

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4. Is it hinted or stated in the medical record that the admission was *medication-related* (including non-compliance)?
   Yes → P (possibly medication-related)
   No → NQ

5. Might (side) effects of the medications the patient was taking (prescribed or non-prescribed) prior to hospitalisation have caused the admission (including over-treatment)?
   Yes → P
   No →NQ
   NOTE: An admission caused by side effects of appropriate medication treatment should be classified as *possibly* medication-related.

6. Are there abnormal laboratory results or vital signs that could be *medication-related* and might have caused the admission?
   Yes → P
   No → NQ

7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?
   Yes → P
   No → NQ

8. Did the patient have any *previously* diagnosed untreated or suboptimally treated (e.g. dose too low) indications that might have caused the admission?
   Yes → P
   No → NQ

9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
   Yes → P
   No → NQ

10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?
    Yes → P
    No → P (the tool has not been able to rule out that the admission is medication-related)

AT-HARM10 – Examples

Assessment Tool for identifying Hospital Admissions Related to Medications

Representative examples of when a question should be answered "Yes" or "No".

1. Was the admission caused by an *infection* or a previously *undiagnosed* disease (e.g. diabetes or heart failure) that is *not medication-related*?

   Yes: A patient admitted because of pneumonia that was *not related* to the patient's *medications*.

   Yes: A patient admitted because of rectal bleeding found, after investigation, to have been caused by a tumour.

   Yes: A patient admitted with an unclear diagnosis and new symptoms. The symptoms cannot be explained by the patient's current medications.

   No: A patient receiving immunosuppressive treatment admitted with infection.

   No: A patient admitted with new symptoms indicating heart failure (oedema, shortness of breath) and a history of excessive use of non-steroidal anti-inflammatory drugs (NSAIDs).

2. Was the admission caused by progression of a previously diagnosed disease that is *not medication-related*?

   NOTE: Appropriateness of medication treatment should only be considered in relation to this question to determine whether the admission is primarily caused by disease progression (*unlikely* MRA) or suboptimal medication treatment or use (*possible* MRA, question 4-10).

   Yes: A patient admitted because of progression of cancer that is not related to the patient's medications.

   Yes: A patient admitted because of exacerbation of congestive heart-failure, which worsened despite optimal treatment (the medication therapy seems to follow the applicable treatment guidelines) and with no signs of non-compliance.

   No: A diabetic patient admitted because of hyperglycaemia without other reason for admission (hyperglycaemia should never lead to admission in a patient that is optimally treated).

3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies (e.g. car accident, wasp allergy, alcohol excess, mushroom poisoning) that are *not medication-related*?

   Yes: A patient admitted because of alcohol intoxication or a car accident that was *not related* to the use of the patient's *medications*.

   No: A patient admitted because of alcohol intoxication worsened by the concomitant use of sedatives.

4. Is it hinted or stated in the medical record that the admission is *medication-related* (including non-compliance)?

   Yes: A physician states in the discharge note that the patient was admitted because of constipation caused by the lack of laxative therapy during treatment with a strong opioid.

   Yes: A patient admitted because of an epileptic seizure and a note in the medical records that the patient is known to be non-compliant.

5. Might (side) effects of the medications the patient was taking (prescribed or non-prescribed) prior to hospitalisation have caused the admission (including over-treatment)?

   NOTE: An admission caused by side effects of appropriate medication treatment should be classified as *possibly* medication-related.

   Yes: A patient admitted with gastric bleeding who uses acetylsalicylic acid to prevent thrombotic events (regardless of the presence of a correct indication and the use of a proton pump inhibitor for gastric protection).

   Yes: A patient admitted because of lactic acidosis after continuing medication with metformin while experiencing dehydrating stomach flu.

   Yes: A patient who uses antihypertensive medication and was admitted due to a fall caused by orthostatic hypotension.

6. Are there abnormal laboratory results or vital signs that could be *medication-related* and might have caused the admission?

   Yes: A patient admitted with a serum digoxin concentration of 3.4 nmol/L (toxic concentration) which may have been the cause for admission.

   Yes: A patient admitted because of hypokalaemia (s-potassium < 3.5 mmol/L) and prescribed a diuretic.

   Yes: A patient with epilepsy admitted with seizures and prescribed a seemingly adequate dose of carbamazepine but with a measured plasma concentration that is too low.

7. Was there any *drug-drug interaction* or *drug-disease interaction* (i.e. a contraindication) that might have caused the admission?

   Yes: A patient admitted because of gastrointestinal bleeding who was taking diclofenac and warfarin in combination before admission.

   Yes: A patient admitted because of serotonin syndrome who was taking tramadol, citalopram and mirtazapine.

Yes: A patient, previously diagnosed with bilateral renal artery stenosis, admitted because of acute renal failure after taking an ACE inhibitor.

Yes: A patient with dementia, who has recently been prescribed an anticholinergic medication (e.g. hydroxyzine), admitted with confusion.

8. Did the patient have any, *previously* diagnosed, untreated or suboptimally treated (e.g. dose too low) indications that might have caused the admission?

   Yes: A patient diagnosed with congestive heart failure, who was taking only a starting dose of ACE-inhibitor (unjustifiably low dose), admitted because of fluid retention and dyspnoea.

   Yes: A patient admitted because of a hip fracture who had a prior diagnosis of osteoporosis but was not taking osteoporosis prophylaxis.

9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?

   Yes: A patient admitted with worsening asthma who was found to be unable to use the inhalers correctly.

   Yes: A patient admitted with palpitations who was found to be unable to swallow tablets and had been crushing slow-release antihypertensive tablets that should have been swallowed whole to retain their slow-release effects.

10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?

    Yes: A patient whose prednisolone treatment has been discontinued too abruptly admitted with nausea, vomiting and diarrhoea.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5-6, 7-8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5, 7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5, 7
	5b	D;V	Describe eligibility criteria for participants.	5, 7
	5c	D;V	Give details of treatments received, if relevant.	-
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	Prev study
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Prev study
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6-7
	10c	V	For validation, describe how the predictions were calculated.	8
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6-7,8
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	7
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11-12
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Prev studies
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	13
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	11-12
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	-
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	D	Explain how to the use the prediction model.	10, Fig 1
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	9, 10, 13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	-
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	18-19
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14,18
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14-17
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-18
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	20
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	19

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.