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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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Complete List of Authors:	Glans, Maria; Lund University, Center for Primary Health Care Research, Department of Clinical Sciences, Malmö; Region Skåne, Kristianstad-Hässleholm Hospitals, Department of Medications Kempen, Thomas; Uppsala University, Department of Pharmacy; Uppsala County Council, Primary Care and Health Jakobsson, Ulf; Lund University, Center for Primary Health Care Research, Department of Clinical Sciences, Malmö Kragh Ekstam, Annika; Region Skåne, Kristianstad-Hässleholm Hospitals, Department of Orthopaedics Bondesson, Åsa; Region Skåne, Department of Medicines Management and Informatics; Lund University, Center for Primary Health Care Research, Department of Clinical Sciences, Malmö Midlöv, Patrik ; Lund University, Center for Primary Health Care Research, Department of Clinical Sciences, Malmö
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4 1 **Identifying older adults at increased risk of medication-related readmission to**
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8 2 **hospital within 30 days of discharge - development and validation of a risk**
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12 3 **assessment tool**
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15 4 *Maria Glans^{*,1,2}, Thomas Gerardus Hendrik Kempen^{3,4}, Ulf Jakobsson¹, Annika Kragh Ekstam⁵, Åsa*
16
17 *Bondesson^{1,6}, Patrik Midlöv¹*
18

19
20 6 ¹ Center for Primary Health Care Research, Department of Clinical Sciences Malmö, Lund University,
21
22 Malmö, Sweden
23

24
25 8 ² Department of Medications, Kristianstad-Hässleholm Hospitals, Region Skåne, Kristianstad, Sweden
26

27
28 9 ³ Department of Pharmacy, Uppsala University, Uppsala, Sweden
29

30
31 10 ⁴ Primary Care and Health, Uppsala County Council, Uppsala, Sweden
32

33
34 11 ⁵ Department of Orthopaedics, Kristianstad-Hässleholm Hospitals, Region Skåne, Kristianstad,
35
36 Sweden
37

38
39 13 ⁶ Department of Medicines Management and Informatics in Skåne County, Region Skåne,
40
41 Kristianstad, Sweden
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43
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45
46
47 16 * Corresponding author:
48

49
50 17 Maria Glans
51

52
53 18 E-mail: maria.glans@med.lu.se
54

55
56 19 Postal address: Center for Primary Health Care Research, Department of Clinical Sciences, Malmö
57

58
59 20 Lund University, Clinical Research Center, Box 50332, 20213 Malmö, Sweden
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4
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10 23 **KEYWORDS**
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14 25 factors; Risk assessment
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1617
18 26
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2021 27 **ABSTRACT**
2223
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25 28 **Objective**
2627
28 29 To develop and validate a risk assessment tool aiming to identify older adults (≥ 65 years) at
29
30 30 increased risk of possibly medication-related readmission to hospital within 30 days of discharge.
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3233
34 31 **Methods**
3536
37 32 The development cohort (n=720) was admitted to a hospital in the south of Sweden during 2017
38
39 33 whereas the validation cohort (n=892) was admitted to a hospital in the mid-eastern part of Sweden
40
41 34 during 2017-2018. Variables known at first admission and individually associated with possibly
42
43 35 medication-related readmission were used when developing the risk assessment tool. The included
44
45 36 variables were assigned points and Youden's index was used to decide a threshold score. The risk
46
47 37 score was calculated for all individuals in both cohorts. ROC-curves were plotted, and c-indexes were
48
49 38 calculated as well as Hosmer and Lemeshow goodness-of-fit, Nagelkerke R^2 , sensitivity, specificity,
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51 39 and positive and negative predictive values.
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40 Results

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

45 Conclusion

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

52 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

63 INTRODUCTION

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

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

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

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

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3 88 discharge. If such a tool was available, interventions aiming to prevent readmission could be
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5 89 implemented based on the risk in the individual patient (15). This could make it possible to not only
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7 90 increase patient safety but also relocate some resources to other areas within healthcare (18).
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12 13 14 92 **OBJECTIVE**

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17 93 The aim of this study was to develop and validate a risk assessment tool that can be used to identify
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19 94 older adults (≥ 65 years) at increased risk of possibly medication-related readmission to hospital
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21 95 within 30 days of discharge.
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26 27 28 97 **METHODS**

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31 98 This study is reported according to the transparent reporting of a multivariable prediction model for
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33 99 individual prognosis or diagnosis (TRIPOD) statement (15).
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36 37 100 **Setting**

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40 101 Sweden is divided into 21 regions and 290 municipalities (19). Primary and hospital care is provided
41
42 102 by the regions while nursing care, in the community or in nursing homes, is provided by the local
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44 103 municipalities. When it comes to planning patient care after hospital discharge, hospital and
45
46 104 municipal care are expected to collaborate (20).
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50 105 According to Swedish regulations (21), medication reconciliation should be performed by the
51
52 106 attending physician when patients aged 75 years and older using five medications or more are
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54 107 admitted to hospital. If medication-related problems are present, the medication reconciliation
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56 108 should be followed by a medication review which could or could not be performed interdisciplinary
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58 109 (i.e. involving a geriatrician or a clinical pharmacist). Unfortunately, adherence to these regulations
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3 110 seems generally low (22) with only about 15% of patients aged 75 years and older receiving a
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5 111 medication reconciliation and/or medication review during their hospital stay (22).
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8 112 **Patient and public involvement**

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12 113 Patients or the public were not involved in this study.
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14 114 **Development of the risk assessment tool**

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18 115 The risk assessment tool was developed using anonymised data and results from our previously
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20 116 published retrospective studies (10, 23) where further details on the methods of data collection can
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22 117 be found.
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25 118 **Study sample and procedure**

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29 119 The study was conducted at Kristianstad hospital, which is an emergency hospital with 255 beds
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31 120 situated in Skåne county in the south of Sweden. The study population, which is further referred to
32
33 121 as the development cohort, consisted of randomly selected patients (n=720), aged 65 years and
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35 122 older, who had been admitted to Kristianstad hospital for at least 24 hours in 2017. Patients were
36
37 123 admitted to one of the following departments: internal medicine, infectious disease, general
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39 124 surgery, orthopaedics, or ear/nose/throat. The study group (n=360) was readmitted within 30 days
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41 125 of discharge while the comparison group (n=360) was not. Variables were collected from electronic
42
43 126 health records in an unblinded yet standardised and objective manner, as previously described (23).
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46
47 127 In total 143 of 360 readmissions (39.7%) were assessed as being possibly medication-related (10).
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49 128 Assessments were made using the Assessment Tool for identifying Hospital Admissions Related to
50
51 129 Medication (AT-HARM10), a validated tool to distinguish between admissions that are possibly and
52
53 130 unlikely medication-related (24). With AT-HARM10 a possibly medication-related
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56 131 (re-)admission is defined as being either caused by or significantly contributed to by a medication-
57
58 132 related problem (for further details see Appendix 1). Preliminary assessments, made by the first
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3 133 author in an unblinded fashion, were reviewed, revised, and finalised by an experienced geriatrician.

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5 134 For further details on the assessment process see our previous publication (10).

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8 135 Through multiple logistic regression analysis (stepwise backward) individual risk factors associated
9
10 136 with all-cause readmission, possibly medication-related readmission, and unlikely medication-
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12 137 related readmission within 30 days of discharge were identified, as described in our previous
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15 138 publications (10, 23).

16 17 18 139 Variables included

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21 140 The risk assessment tool was developed using variables identified by comparing patients with a
22
23 141 possibly medication-related readmission (n=143) with those that did not have a possibly medication-
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25 142 related readmission (n=577) (i.e. patients with an unlikely medication-related readmission (n=217)
26
27 143 and patients not readmitted (n=360)). Only variables known at first admission to hospital were
28
29 144 included in the development of the risk assessment tool.

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33 145 Variables shown to be associated with possibly medication-related readmission, through multiple
34
35 146 logistic regression analysis, were chosen to be included in the final risk assessment tool. For
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37 147 continuous variables, categorical variables were created based on comparisons between groups.

38 39 40 41 148 Data analysis

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44 149 Based on the odds ratios of the individual variables in the final multiple logistic regression model,
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46 150 suitable weighting and scoring were decided upon for each of the included variables. A risk score,
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48 151 which summarised the points assigned to each of the variables included, was calculated for all the
49
50 152 included individuals. Finally, a new logistic regression analysis was performed with possibly
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52 153 medication-related readmission as the dependent variable and the risk score as the test variable,
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54 154 saving the probabilities for further analysis. To estimate the quality of the model Hosmer and
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56 155 Lemeshow goodness-of-fit was calculated as well as Nagelkerke R².

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3 156 A ROC-curve was plotted using the saved probabilities and the area under the ROC-curve (c-index)
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5 157 was calculated giving a measure of how well the tool predicts possibly medication-related
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7 158 readmission.

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10 159 To decide upon a suitable threshold value in the risk assessment tool Youdens' index ($J = \text{Sensitivity} +$
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12 160 $\text{Specificity} - 1$) was calculated for all steps in the risk score. Cross-tabulation was used to calculate
13
14 161 sensitivity, specificity, and positive and negative predictive values as well as to identify the number
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16 162 of correctly predicted patients.

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20 163 Statistical analyses were performed using IBM SPSS Statistics version 27.
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23 164 External validation of the risk score

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26 165 To check the predictive ability of the risk score, as well as its precision and usefulness in other
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28 166 populations, we performed an external validation using data from the Medication Reviews Bridging
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30 167 Healthcare (MedBridge) trial (25).
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34 168 Study sample and procedure

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37 169 The MedBridge trial (25, 26) was a randomised clinical trial conducted at four hospitals (Uppsala,
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39 170 Gävle, Västerås, and Enköping) in the mid-eastern part of Sweden. The aim of the trial was to study
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41 171 the effects of hospital-based medication reviews including post-discharge follow-up on the use of
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43 172 healthcare resources in older adults (≥ 65 years), compared with hospital-based reviews and usual
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45 173 care only.

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49 174 Included participants were admitted to a medical ward at one of the four included hospitals for at
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51 175 least 24 hours within the time-frame 6th of February 2017 to the 19th of October 2018. Out of the
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53 176 2637 patients included in the trial, 1745 were included in one of the two medication review groups,
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55 177 and 892 patients were included in the usual care group. Outcomes measured in the trial included
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3 178 readmission to hospital within 30 days of discharge and possibly medication-related readmission as
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5 179 assessed with AT-HARM10 (24).
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8 180 To make sure the medication review interventions in the MedBridge trial could not affect the result
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10 181 of the validation, the MedBridge control group, i.e. the 892 patients receiving usual care, was chosen
11
12 182 to create the validation cohort in which the developed risk assessment tool was validated. In the
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14 183 validation cohort (n=892) 132 patients were readmitted within 30 days of discharge and 54 of these
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16 184 readmissions (40.9%) were assessed as being possibly medication-related.
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20 185 Data analysis

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23 186 A multiple logistic regression analysis with the variables included in the risk assessment tool was
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25 187 performed in the validation cohort, comparing patients with a possibly medication-related
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27 188 readmission (n=54) and those that did not have a possibly medication-related readmission (n=838)
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29 189 (i.e. those with an unlikely medication-related readmission (n=78) and those that were not
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31 190 readmitted within 30 days of discharge (n=760)). To estimate the quality of the model, Hosmer and
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33 191 Lemeshow goodness-of-fit was calculated as well as Nagelkerke R².
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38 192 The risk score was calculated for each of the individuals in the validation cohort and a new logistic
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40 193 regression analysis was performed with possibly medication-related readmission as the dependent
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42 194 variable and the risk score as the test variable. Probabilities were saved and used to plot a ROC-
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44 195 curve where the c-index was calculated giving an estimate of the predictive ability of the risk
45
46 196 assessment tool in this external population.
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49 197 Cross-tabulation was used at each of the steps in the risk score to calculate sensitivity, specificity,
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51 198 and positive and negative predictive values. Furthermore, the number of correctly predicted patients
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53 199 was identified.
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57 200 Statistical analysis was performed using IBM SPSS Statistics version 27.
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202 RESULTS

203 Development of the risk assessment tool

204 Variables included

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

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

215 **Table 1. Final multiple logistic regression model from the model development dataset with**
 216 **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
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217 *Abbreviations: OR – Odds Ratio, CI – Confidence Interval*

218 *^aAdjusted for gender and age.*

219 *Hosmer Lemeshow goodness of fit test p-value: 0.369. Nagelkerke R²: 0.113.*

220 *Significant p-values are indicated in bold.*

221

222 Developing the risk score

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

229 The model showed good calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000
 230 and Nagelkerke R² of 0.118. The calculated area under the risk score ROC-curve (c-index) was 0.69
 231 (95%CI 0.64-0.74).

232

233 FIGURE 1 – the HOME Score

234

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

238

239 **Table 2. Youden's Index calculated for each step in the risk score in order to find a suitable**240 **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

241

242 A threshold score of ≥ 4 points was finally chosen as the threshold score. The choice was based on
 243 the desire to identify as many patients at increased risk of possibly medication-related readmission
 244 as possible, i.e. sensitivity rather than specificity should be as high as possible. At the threshold score
 245 (≥ 4 points) sensitivity was 76%, specificity 54%, positive predictive value 29%, and negative
 246 predictive value 90% (Table 3). The number of correctly predicted patients was 108 (out of 143).

247

248 **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 \geq 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 \geq 5		
Sensitivity, %	41	43
Specificity, %	83	80
Positive predictive value, %	38	12
Negative predictive value, %	85	96
Number of correctly predicted patients	59	23

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250

251 External validation of the risk assessment tool

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

254 Logistic regression analysis in the validation cohort, with *Possibly medication-related readmission* as
 255 the dependent variable and *HOME score* as the test variable, showed good calibration with a
 256 Hosmer and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R² of 0.051.

257

258 **Table 4. Comparison^a of variables between groups in the development and validation cohort**

Predictor	Development cohort			Validation cohort		
	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 \geq 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 \geq 5, %	87	71	<0.001	91	81	0.077
Emergency admission, %	97	89	0.002	100	96	0.150

259 *Abbreviations: PMRR – Possibly Medication-Related Readmission*

260 ^aA χ^2 -test was used for analysis in all cases, ^bComparison group = Patients not readmitted and
 261 patients with an unlikely medication-related readmission

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

263

264 The c-index of the HOME Score was 0.65 (CI95% 0.57-0.72, p-value < 0.001) in the validation cohort.

265 The risk score, with the cut-off point set at \geq 4 points, showed a nonsignificant difference between
 266 groups (p-value 0.051). At this threshold score (\geq 4) sensitivity was 63%, specificity 51%, positive

267 predictive value 8%, and negative predictive value 96% (Table 3). The number of correctly predicted

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3 268 patients was 34 (out of 54). With the cut-off point set at ≥ 5 points there was a significant difference
4
5 269 between groups (p value < 0.001). Sensitivity was 43%, specificity 80%, positive predictive value 12%
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7 270 and negative predictive value 96%. The number of correctly predicted patients was 23 (out of 54)
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10 271 (Table 3).
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272

273 DISCUSSION

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

281 Comparisons to other studies

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

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

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3 291 The tool was derived in a multicentre, prospective cohort study in the UK. In total 818 patients
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5 292 discharged from five UK teaching hospitals between 2013 and 2015 were included. The PRIME tool
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7 293 was internally validated using bootstrapping and the c-index was 0.69 before and 0.66 after
8
9 294 validation. Hence, compared to the PRIME tool, the HOME Score has a similar predictive ability with
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11 295 a c-index of 0.69 in the development cohort and 0.65 in the validation cohort.
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15 296 **Variables included in the model**

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18 297 The variables included in the HOME Score were identified in our previous studies (10, 23) where we
19
20 298 identified risk factors of all-cause readmission, possibly medication-related readmission, and unlikely
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22 299 medication-related readmission within 30 days of discharge, in patients 65 years and older. We
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24 300 chose to solely include variables known already at admission since research suggests that the
25
26 301 successful reduction of possibly medication-related readmission demands the implementation of
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28 302 actions during the hospital stay (29) as well as at discharge (12) and in transitions of care (14). In
29
30 303 order to do this, patients at increased risk of possibly medication-related readmission need to be
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32 304 identified already at admission. Hence, the HOME Score has an advantage compared to previously
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34 305 developed tools such as the PRIME tool (16), which include factors not known until discharge.
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40 306 **Hospitalisations within the last 12 months ≥ 2**

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43 307 The number of previous hospitalisations is a measure of disease burden and the fact that readmitted
44
45 308 patients are more ill does not really come as a surprise since this has been shown previously (2, 23,
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47 309 28). In a Swedish study from 2022, Naseer et al (30) showed that emergency department visits in
48
49 310 older adults are significantly associated with several variables indicating disease burden, such as
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51 311 number of chronic diseases, number of primary care visits, number of emergency department visits,
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53 312 polypharmacy, and receipt of home care.
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57 313 Naseer et al (31) have also shown that prior healthcare use is associated with emergency
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59 314 department revisits within 30 days, in older adults. Similarly, we have identified previous healthcare
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3 315 use as a risk factor of possibly medication-related readmissions within 30 days of discharge (10)
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5 316 which is why this factor was included in the HOME Score. Prior healthcare use has also been
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7 317 indicated as a risk factor for all-cause readmission (23, 27, 28) and the factor is included in the
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9 318 HOSPITAL Score (27) as well as in the LACE Index (28).
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13 319 Living in own home with home care and/or alone

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16 320 Living in your own home alone is included as a variable in the HOME Score as well as in the PRIME
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18 321 tool (16). Living arrangements have been previously indicated as risk factors for readmission in
19
20 322 several studies. In 2016 Olson et al (32) identified an increased risk of readmission in older men
21
22 323 living in their own home with only their adult children as caregivers. Further, Gruneir et al (33) have
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24 324 shown that patients using high-risk medications have an 80% increased risk of readmission within 30
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26 325 days if discharged to their own home as opposed to a nursing home. However, Naseer et al (31) did
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28 326 not find living alone to be explanatory of emergency department revisits in older adults. They did, on
29
30 327 the other hand, find the receipt of home care to be significantly associated with emergency
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32 328 department revisits in one of the two Swedish regions studied. Similarly, Dahlberg et al (34) have
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34 329 shown that living at home with home care is significantly associated with unplanned (emergency)
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36 330 admission to hospital.
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41 331 When it comes to readmission to hospital, we have previously shown that living in the community
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43 332 with home care is a risk factor for all-cause readmission (23) and in this study further analyses
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45 333 showed that it is also associated with possibly medication-related readmission. This factor is not, to
46
47 334 our knowledge, found in other assessment tools aiming to identify all-cause readmission or possibly
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49 335 medication-related readmission. However, it is part of several comprehensive geriatric assessment
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51 336 tools aiming to identify vulnerability and frailty (35-37). Such comprehensive geriatric assessment
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53 337 tools have also been shown to be predictive of all-cause readmission to hospital within 30 days (35)
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55 338 and 60 days (36) of discharge, in older adults.
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339 Number of medications at admission ≥ 5

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

350 Emergency admission

351 Emergency admission, as opposed to planned admission, has been indicated as a risk factor for 30-
352 day readmission in several studies, including ours (10, 23), and the factor is included in both the
353 HOSPITAL Score (27) and the LACE Index (28).
354 In the study by Dahlberg et al (34) the only social factor significantly associated with unplanned
355 hospital admission was living at home with home care. Furthermore, in our previous study, we
356 showed that older adults with a possibly medication-related readmission who lived alone were more
357 often readmitted due to an unsustainable home situation than those living with someone (10). Since
358 living with home care and living alone are also indicated as risk factors for all-cause and possibly
359 medication-related readmissions, this indicates that these readmitted older adults need closer
360 supervision after discharge. At the very least they need better planning before discharge. To achieve
361 this, the collaboration between hospital, primary, and municipal care needs to improve (12, 14).

362 **Implications for clinical use**

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

370 **Strengths and limitations**

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

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

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

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3 385 result depends on the person conducting them. This could be considered a weakness. However, the
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5 386 fact that the amount of possibly medication-related readmissions was almost the same in the
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7 387 development and validation cohort (40% in the development cohort and 41% in the validation
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9 388 cohort) indicates that this may not be a big issue.

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13 389 In the development cohort, included patients were admitted to medical as well as surgical
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15 390 departments whereas patients in the validation cohort were admitted solely to medical wards. This
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17 391 could have affected the results and further validations of the HOME Score are needed in order to
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19 392 establish its clinical usefulness in different departments as well as in other countries.

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23 24 25 26 394 **CONCLUSION**

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29 395 The HOME Score can be used to identify older adults at increased risk of possibly medication-related
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31 396 readmission within 30 days of discharge. The tool is easy to use and includes variables that are
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33 397 readily available in electronic health records at admission, thus making it possible to implement risk-
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35 398 reducing activities during the hospital stay as well as at discharge and in transitions of care. These
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37 399 activities could likely help increase patient safety as well as be beneficial to the health economy.
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40 400 Further studies are needed to test these hypotheses.

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55
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57
58
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78 409 **STATEMENTS**
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11 410 **Competing interests**
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15 411 The authors declare that they have no competing interests.
1617
18 412 **Author contributions**
1920
21 413 All authors have contributed to the design of this study. MG collected, interpreted, and analysed the
22
23 414 data with the support of the other authors. The first draft of the manuscript was completed by MG
24
25 415 after which it was critically read and commented on by the other authors. All authors have read and
26
27 416 approved the final manuscript.
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42 422 or in writing the manuscript.
43
44
4546 423 **Ethics statement**
4748
49 424 Ethical approval was applied for and approved by the Swedish Ethics Review Authority (Dnr 2021-
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51 425 06612-01).
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426 Data Availability Statement

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

432

433 FIGURE LEGEND

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

438

439 SUPPORTING INFORMATION

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

443

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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		
<i>A score of 4 or more denotes increased risk</i>		

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

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2
3 5. Might (side) effects of the medications the patient was taking (prescribed or non-prescribed)
4 prior to hospitalisation have caused the admission (including over-treatment)?

5
6 Yes → P

7
8 No → NQ

9 **NOTE:** An admission caused by side effects of appropriate medication treatment should be
10 classified as *possibly* medication-related.
11
12
13

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

16
17 Yes → P

18
19 No → NQ
20
21

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

24
25 Yes → P

26
27 No → NQ
28
29

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

32
33 Yes → P

34
35 No → NQ
36
37

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

40
41 Yes → P

42
43 No → NQ
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45

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

47
48 Yes → P

49 No → P (the tool has not been able to rule out that the admission is medication-related)
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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.

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

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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.

1
2
3 **Yes:** A patient, previously diagnosed with bilateral renal artery stenosis, admitted because of
4 acute renal failure after taking an ACE inhibitor.

5
6 **Yes:** A patient with dementia, who has recently been prescribed an anticholinergic medication
7 (e.g. hydroxyzine), admitted with confusion.
8
9

- 10
11 8. Did the patient have any, *previously* diagnosed, untreated or suboptimally treated (e.g. dose too
12 low) indications that might have caused the admission?
13

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

16 **Yes:** A patient admitted because of a hip fracture who had a prior diagnosis of osteoporosis but
17 was not taking osteoporosis prophylaxis.
18
19

- 20
21
22 9. Was the patient admitted because of a problem with the dosage form or pharmaceutical
23 formulation (i.e. failure to receive the medication)?
24

25 **Yes:** A patient admitted with worsening asthma who was found to be unable to use the inhalers
26 correctly.
27

28 **Yes:** A patient admitted with palpitations who was found to be unable to swallow tablets and
29 had been crushing slow-release antihypertensive tablets that should have been swallowed whole
30 to retain their slow-release effects.
31
32

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35 10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?
36

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

1
2 *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
3 denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD
4 Explanation and Elaboration document.
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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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4 1 **Identifying older adults at increased risk of medication-related readmission to**
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8 2 **hospital within 30 days of discharge - development and validation of a risk**
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12 3 **assessment tool**
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15 4 *Maria Glans^{*,1,2}, Thomas Gerardus Hendrik Kempen^{3,4}, Ulf Jakobsson¹, Annika Kragh Ekstam⁵, Åsa*
16
17 5 *Bondesson^{1,6}, Patrik Midlöv¹*

18
19
20 6 ¹ Center for Primary Health Care Research, Department of Clinical Sciences Malmö, Lund University,
21
22
23 7 Malmö, Sweden

24
25
26 8 ² Department of Medications, Kristianstad-Hässleholm Hospitals, Region Skåne, Kristianstad, Sweden

27
28
29 9 ³ Department of Pharmacy, Uppsala University, Uppsala, Sweden

30
31
32 10 ⁴ Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical
33
34 11 Sciences, Utrecht University, Utrecht, the Netherlands

35
36
37 12 ⁵ Department of Orthopaedics, Kristianstad-Hässleholm Hospitals, Region Skåne, Kristianstad,
38
39 13 Sweden

40
41
42 14 ⁶ Department of Medicines Management and Informatics in Skåne County, Region Skåne,
43
44 15 Kristianstad, Sweden

45
46
47 16
48
49 17 * Corresponding author:

50
51
52 18 Maria Glans

53
54
55 19 E-mail: maria.glans@med.lu.se

56
57
58 20 Postal address: Center for Primary Health Care Research, Department of Clinical Sciences, Malmö
59
60

1
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3 21 Lund University, Clinical Research Center, Box 50332, 20213 Malmö, Sweden
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9 23 **Word count:** 4886 words
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12 24
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15 25 **KEYWORDS**

16
17
18 26 Older adults; Transitions in care; Patient discharge; Patient readmission; Risk factors; Risk
19 27 assessment
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25 26 27 29 **ABSTRACT**

28 29 30 30 **Objective**

31 31 Developing and validating a risk assessment tool aiming to identify older adults (≥ 65 years) at
32 32 increased risk of possibly medication-related readmission to hospital within 30 days of discharge.
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39 33 **Design**

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42 34 Retrospective cohort study.
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46 35 **Setting**

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49 36 The risk score was developed using data from a hospital in southern Sweden and validated using
50 37 data from four hospitals in the mid-eastern part of Sweden.
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54 38 **Participants**

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57 39 The development cohort (n=720) was admitted to hospital during 2017 whereas the validation
58 40 cohort (n=892) was admitted during 2017-2018.
59
60

41 Measures

42 The risk assessment tool aims to predict possibly medication-related readmission to hospital within
43 30 days of discharge. Variables known at first admission and individually associated with possibly
44 medication-related readmission were used in development. The included variables were assigned
45 points and Youden's index was used to decide a threshold score. The risk score was calculated for all
46 individuals in both cohorts. Area under the ROC-curve (c-index) was used to measure the
47 discrimination of the developed risk score. Sensitivity, specificity, and positive and negative
48 predictive values were calculated using cross-tabulation.

49 Results

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

54 Conclusion

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

61

62 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

73 INTRODUCTION

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

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

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3 86 reactions, adverse drug events, or drug-drug reactions others measure readmissions related to
4
5 87 medication-related problems, thus including all the above-mentioned problems (8).
6
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8 88 Many medication-related readmissions may be possible to prevent, even though the proportion
9
10 89 deemed preventable also differs between studies (8), again, due to differences in methods used.
11
12
13 90 According to previous research, preventive measures should aim to improve medication use as well
14
15 91 as transitions of care (11, 12) and are best performed by combining several minor activities into
16
17 92 concepts (12, 13). These activities should preferably include interdisciplinary actions during the
18
19 93 hospital stay and at discharge (12) as well as collaboration between hospital, primary, and municipal
20
21 94 care in transitions of care (14).
22
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25 95 To effectively implement interventions, healthcare personnel need to be able to identify patients at
26
27 96 increased risk of medication-related readmission. This could preferably be done by using a risk
28
29 97 assessment tool or risk score (15). Some risk assessment tools linked to medication-related
30
31 98 readmission have been developed (16, 17). The PRIME tool, developed by Parekh et al (16),
32
33 99 identifies older adults at increased risk of medication-related harm requiring healthcare use within
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36 100 eight weeks of discharge while the decision support tool developed by Olson et al (17) predicts the
37
38 101 risk of readmission in older adults using high-risk medication regimens. None of these tools have
39
40 102 been validated in an external population or tested in a setting other than the one where it was
41
42 103 developed.
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45 104 To our knowledge, there is no risk assessment tool available that specifically aims to identify older
46
47 105 adults at increased risk of possibly medication-related readmission to hospital within 30 days of
48
49 106 discharge. If such a tool was available, interventions aiming to prevent readmission could be
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51 107 implemented based on the risk in the individual patient (15). This could make it possible to not only
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53 108 increase patient safety but also relocate some resources to other areas within healthcare.
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110 OBJECTIVE

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

115 METHODS

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

118 Setting

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

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

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

132 Patient and public involvement

133 Patients or the public were not involved in this study.

134 Development of the risk assessment tool

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

138 Study sample and procedure

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

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

1
2
3 155 interferes with desired patient outcomes” (23). This means that medication-related problems
4
5 156 involve not only adverse drug reactions or adverse drug events but also problems such as
6
7 157 inappropriate prescribing, non-compliance, and problems related to over-the-counter medications
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9
10 158 (23). For further details on AT-HARM10, see Appendix 1.
11

12
13 159 Preliminary assessments, made by the first author in an unblinded fashion, were reviewed, revised,
14
15 160 and finalised by an experienced geriatrician. For further details on the assessment process see our
16
17 161 previous publication (10).
18

19
20 162 Through multiple logistic regression analysis (stepwise backward) individual risk factors associated
21
22 163 with all-cause readmission, possibly medication-related readmission, and unlikely medication-
23
24 164 related readmission within 30 days of discharge were identified, as described in our previous
25
26 165 publications (10, 22).
27
28

30 166 Variables included

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33 167 The risk assessment tool was developed using variables identified by comparing patients with a
34
35 168 possibly medication-related readmission (n=143) with those that did not have a possibly medication-
36
37 169 related readmission (n=577) (i.e. patients with an unlikely medication-related readmission (n=217)
38
39 170 and patients not readmitted (n=360)). Only variables known at first admission to hospital were
40
41 171 included in the development of the risk assessment tool.
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44
45 172 Variables shown to be associated with possibly medication-related readmission, through multiple
46
47 173 logistic regression analysis, were chosen to be included in the final risk assessment tool. For
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49 174 continuous variables, categorical variables were created based on comparisons between groups.
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52 175 Data analysis

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56 176 Based on the odds ratios of the individual variables in the final multiple logistic regression model,
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58 177 suitable weighting and scoring were decided upon for each of the included variables. A risk score,
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3 178 which summarised the points assigned to each of the variables included, was calculated for all the
4
5 179 included individuals. Finally, a new logistic regression analysis was performed with possibly
6
7 180 medication-related readmission as the dependent variable and the risk score as the test variable,
8
9 181 saving the probabilities for further analysis. To estimate the quality of the model Hosmer and
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11
12 182 Lemeshow goodness-of-fit was calculated as well as Nagelkerke R².

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14
15 183 A ROC-curve was plotted using the saved probabilities and the area under the ROC-curve (c-index)
16
17 184 was calculated giving a measure of how well the tool predicts possibly medication-related
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19 185 readmission.

20
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22 186 To decide upon a suitable threshold value in the risk assessment tool Youdens' index ($J = \text{Sensitivity} +$
23
24 187 $\text{Specificity} - 1$) was calculated for all steps in the risk score. Cross-tabulation was used to calculate
25
26 188 sensitivity, specificity, and positive and negative predictive values as well as to identify the number
27
28 189 of correctly predicted patients.

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32 190 Statistical analyses were performed using IBM SPSS Statistics version 27.

33 34 35 191 **External validation of the risk score**

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37
38 192 To check the predictive ability of the risk score, as well as its precision and usefulness in other
39
40 193 populations, we performed an external validation using data from the Medication Reviews Bridging
41
42 194 Healthcare (MedBridge) trial (25, 26).

43 44 45 46 195 **Study sample and procedure**

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49 196 The MedBridge trial (25, 26) was a randomised clinical trial conducted at four hospitals (Uppsala,
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51 197 Gävle, Västerås, and Enköping) in the mid-eastern part of Sweden. The aim of the trial was to study
52
53 198 the effects of hospital-based medication reviews including post-discharge follow-up on the use of
54
55 199 healthcare resources in older adults (≥ 65 years), compared with hospital-based reviews and usual
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57 200 care only.

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3 201 Included participants were admitted to a medical ward at one of the four included hospitals for at
4
5 202 least 24 hours within the time-frame 6th of February 2017 to the 19th of October 2018. Out of the
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7 203 2637 patients included in the trial, 1745 were included in one of the two medication review groups,
8
9 204 and 892 patients were included in the group receiving usual care. Outcomes measured in the trial
10
11 205 included readmission to hospital within 30 days of discharge and possibly medication-related
12
13 206 readmission as assessed with AT-HARM10 (24). For further details on the population and methods of
14
15 207 data collection used in the MedBridge trial, see Kempen et al (25).
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19 208 To make sure the medication review interventions in the MedBridge trial could not affect the result
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21 209 of the validation, the MedBridge control group, i.e. the 892 patients receiving usual care, was chosen
22
23 210 to create the validation cohort in which the developed risk assessment tool was validated. In the
24
25 211 validation cohort (n=892) 132 patients were readmitted within 30 days of discharge and 54 of these
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27 212 readmissions (40.9%) were assessed as being possibly medication-related.
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31 213 Data analysis

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35 214 A multiple logistic regression analysis with the variables included in the risk assessment tool was
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37 215 performed in the validation cohort, comparing patients with a possibly medication-related
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39 216 readmission (n=54) and those that did not have a possibly medication-related readmission (n=838)
40
41 217 (i.e. those with an unlikely medication-related readmission (n=78) and those that were not
42
43 218 readmitted within 30 days of discharge (n=760)). To estimate the quality of the model, Hosmer and
44
45 219 Lemeshow goodness-of-fit was calculated as well as Nagelkerke R².
46
47
48
49 220 The risk score was calculated for each of the individuals in the validation cohort and a new logistic
50
51 221 regression analysis was performed with possibly medication-related readmission as the dependent
52
53 222 variable and the risk score as the test variable. Probabilities were saved and used to plot a ROC-
54
55 223 curve where the c-index was calculated giving an estimate of the predictive ability of the risk
56
57 224 assessment tool in this external population.
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225 Cross-tabulation was used at each of the steps in the risk score to calculate sensitivity, specificity,
226 and positive and negative predictive values. Furthermore, the number of correctly predicted patients
227 was identified.

228 Statistical analysis was performed using IBM SPSS Statistics version 27.

229

230 RESULTS

231 Development of the risk assessment tool

232 Variables included

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

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

240 The mean number of hospitalisations in patients with a possibly medication-related readmission was
241 1.94 and the median was 2. The mean number in the comparison group (including patients not
242 readmitted and those with a readmission unlikely related to medications) was 1.67 and the median
243 was 1. Hence, the categorical variable was set as *Hospitalisations within the last 12 months ≥ 2* .

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

247 was 10 and 7 respectively. Both the categorical variable *Number of medications at admission* ≥ 5 and
 248 *Number of medications at admission* ≥ 10 were tested in the multiple logistic regression model. Both
 249 variables showed similar odds ratios (2.20 with number of medications ≥ 5 and 1.99 with number of
 250 medications ≥ 10) and both had significant p-values (0.005 with number of medications ≥ 5 and
 251 <0.001 with number of medications ≥ 10). Finally, we chose to use the categorical variable *Number of*
 252 *medications at admission* ≥ 5 in the final model (Table 1).

253

254 **Table 1. Final multiple logistic regression model from the model development dataset with**
 255 **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

256 *Abbreviations: OR – Odds Ratio, CI – Confidence Interval*

257 ^a*Adjusted for gender and age.*

258 *Hosmer Lemeshow goodness of fit test p-value: 0.802. Nagelkerke R²: 0.113.*

259 *Significant p-values are indicated in bold.*

260

261 **Developing the risk score**

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

268 The model showed fair calibration with a Hosmer and Lemeshow goodness of fit p-value of 1.000
 269 and Nagelkerke R² of 0.117. The calculated area under the risk score ROC-curve (c-index) was 0.69
 270 (95%CI 0.64-0.74).

271

272 **FIGURE 1 – the HOME Score**

273

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

277

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

Score	Sensitivity	1-Specificity	Specificity	Youden's Index
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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

280

281 A threshold score of ≥ 4 points was finally chosen as the threshold score. The choice was based on
 282 the desire to identify as many patients at increased risk of possibly medication-related readmission
 283 as possible, i.e. sensitivity rather than specificity should be as high as possible. At the threshold score
 284 (≥ 4 points) sensitivity was 76%, specificity 53%, positive predictive value 29%, and negative
 285 predictive value 90% (Table 3). The number of correctly predicted patients was 108 (out of 143).

286

287 **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 \geq 4, n (%)	377 (52)	447 (50)
Patients with possibly medication-related readmission		
HOME Score <4, n (%)	35 (10)	20 (5)
HOME Score \geq 4, n (%)	108 (29)	34 (8)
At HOME Score \geq 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 \geq 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

288

289

290 External validation of the risk assessment tool

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

293 Logistic regression analysis in the validation cohort, with *Possibly medication-related readmission* as
 294 the dependent variable and *HOME score* as the test variable, showed fair calibration with a Hosmer
 295 and Lemeshow goodness of fit p-value of 1.000 and Nagelkerke R² of 0.051.

296

297 **Table 4. Comparison^a of variables between groups in the development and validation cohort**

Predictor	Development cohort			Validation cohort		
	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 \geq 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 \geq 5, %	87	71	<0.001	91	81	0.077
Emergency admission, %	97	89	0.002	100	96	0.150

298 *Abbreviations: PMRR – Possibly Medication-Related Readmission*299 *^aA χ^2 -test was used for analysis in all cases, ^bComparison group = Patients not readmitted and
300 patients with an unlikely medication-related readmission*301 *Significant p-values ($p < 0.05$) are indicated in bold.*

302

303 The c-index of the HOME Score was 0.65 (CI95% 0.57-0.72, p-value < 0.001) in the validation cohort.

304 The risk score, with the cut-off point set at \geq 4 points, showed a nonsignificant difference between
305 groups (p-value 0.051). At this threshold score (\geq 4) sensitivity was 63%, specificity 51%, positive

306 predictive value 8%, and negative predictive value 96% (Table 3). The number of correctly predicted

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2
3 307 patients was 34 (out of 54). With the cut-off point set at ≥ 5 points there was a significant difference
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5 308 between groups (p value < 0.001). Sensitivity was 43%, specificity 80%, positive predictive value 12%
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7 309 and negative predictive value 96%. The number of correctly predicted patients was 23 (out of 54)
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10 310 (Table 3).
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13 311

16 312 **DISCUSSION**

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19
20 313 The risk assessment tool developed in this study, the HOME Score, is the first externally validated
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22 314 risk assessment tool that can be used to identify older adults (≥ 65 years) at increased risk of possibly
23
24 315 medication-related readmission to hospital within 30 days of discharge. The HOME Score was fairly
25
26 316 discriminative of possibly medication-related readmission and showed fair calibration in
27
28 317 development as well as in external validation. The tool is easy to use and includes variables that
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30 318 should be readily available in the electronic health records at admission, thus making it possible to
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32 319 implement risk-reducing activities during the hospital stay as well as at discharge and in transitions
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34 320 of care.
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40 321 **Comparisons to other studies**

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43 322 There have not yet, to our knowledge, been any risk assessment tools developed that are directly
44
45 323 comparable to the HOME Score. However, there are several tools that can be used to identify
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47 324 patients at increased risk of all-cause readmission to hospital within 30 days of discharge, such as the
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49 325 HOSPITAL Score (27), the LACE Index (28), and the PAR-Risk Score (29). Even though the PAR-Risk
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51 326 Score focuses on medications as a risk factor for potentially avoidable hospital readmissions, it does
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53 327 not specifically predict medication-related readmissions. There are, however, a few risk assessment
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55 328 tools related to medication-related healthcare use after discharge, such as the PRIME tool (16) and
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2
3 329 the decision support tool developed by Olson et al (17). None of the above-mentioned tools solely
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5 330 includes factors that are known already at admission as does the HOME Score.
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8 331 The PRIME tool, developed by Parekh et al (16), identifies older patients (≥ 65 years) at increased risk
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10 332 of medication-related harm requiring healthcare use within eight weeks of discharge from hospital.
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12 333 The tool was derived in a multicentre, prospective cohort study in the UK. In total 818 patients
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14 334 discharged from five UK teaching hospitals between 2013 and 2015 were included. The PRIME tool
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16 335 was internally validated using bootstrapping and the c-index was 0.69 before and 0.66 after
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18 336 validation. Hence, compared to the PRIME tool, the HOME Score has a similar predictive ability with
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20 337 a c-index of 0.69 in the development cohort and 0.65 in the validation cohort.
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24 338 With the PRIME tool (16) healthcare use after discharge includes not only hospital readmissions but
25
26 339 also other healthcare use such as visits to the emergency department, in-person or telephone
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28 340 consultations with a general practitioner, or visits to outpatient clinics. This means that the PRIME
29
30 341 tool predicts healthcare use in broader sense than does the HOME Score. Further, medication-
31
32 342 related harm in the PRIME tool is defined as adverse drug reactions and harm arising from non-
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34 343 adherence only while the HOME Score defines medication-related problems more broadly, also
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36 344 including problems such as inappropriate prescribing and problems related to over-the-counter
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38 345 medications (see Appendix 1) (23).
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43 346 **Variables included in the model**

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46 347 The variables included in the HOME Score were identified in our previous studies (10, 22) where we
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48 348 identified risk factors for all-cause readmission, possibly medication-related readmission, and
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50 349 unlikely medication-related readmission within 30 days of discharge, in patients 65 years and older.
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53 350 We chose to solely include variables known already at admission since research suggests that the
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55 351 successful reduction of possibly medication-related readmission demands the implementation of
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57 352 actions during the hospital stay (30) as well as at discharge (12) and in transitions of care (14). In
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59 353 order to do this, patients at increased risk of possibly medication-related readmission need to be
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3 354 identified already at admission. Hence, the HOME Score has an advantage compared to previously
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5 355 developed tools such as the PRIME tool (16), which include factors not known until discharge.
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8 356 Hospitalisations within the last 12 months ≥ 2

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11 357 The number of previous hospitalisations is a measure of disease burden and the fact that readmitted
12
13 358 patients are more ill does not really come as a surprise since this has been shown previously (2, 22,
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15 359 28). In a Swedish study from 2022, Naseer et al (31) showed that emergency department visits in
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17 360 older adults are significantly associated with several variables indicating disease burden, such as
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19 361 number of chronic diseases, number of primary care visits, number of emergency department visits,
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21 362 polypharmacy, and receipt of home care.
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24
25 363 Naseer et al (32) have also shown that prior healthcare use is associated with emergency
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27 364 department revisits within 30 days, in older adults. Similarly, we have identified previous healthcare
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29 365 use as a risk factor of possibly medication-related readmissions within 30 days of discharge (10)
30
31 366 which is why this factor was included in the HOME Score. Prior healthcare use has also been
32
33 367 indicated as a risk factor for all-cause readmission (22, 27, 28) and the factor is included, in some
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35 368 form, in the HOSPITAL Score (27), the LACE Index (28), and the PAR-Risk Score (29).
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40 369 Living in own home with home care and/or alone

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43 370 Living in your own home alone is included as a variable in the HOME Score as well as in the PRIME
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45 371 tool (16). Living arrangements have been previously indicated as risk factors for readmission in
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47 372 several studies. In 2016 Olson et al (33) identified an increased risk of readmission in older men
48
49 373 living in their own home with only their adult children as caregivers. Further, Gruneir et al (34) have
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51 374 shown that patients using high-risk medications have an 80% increased risk of readmission within 30
52
53 375 days if discharged to their own home as opposed to a nursing home. However, Naseer et al (32) did
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55 376 not find living alone to be explanatory of emergency department revisits in older adults. They did, on
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57 377 the other hand, find the receipt of home care to be significantly associated with emergency
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3 378 department revisits in one of the two Swedish regions studied. Similarly, Dahlberg et al (35) have
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5 379 shown that living at home with home care is significantly associated with unplanned (emergency)
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7 380 admission to hospital.

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10 381 When it comes to readmission to hospital, we have previously shown that living in the community
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12 382 with home care is a risk factor for all-cause readmission (22) and in this study further analyses
13
14 383 showed that it is also associated with possibly medication-related readmission. This factor is not, to
15
16 384 our knowledge, found in other assessment tools aiming to identify all-cause readmission or possibly
17
18 385 medication-related readmission. However, it is part of several comprehensive geriatric assessment
19
20 386 tools aiming to identify vulnerability and frailty (36-38). Such comprehensive geriatric assessment
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22 387 tools have also been shown to be predictive of all-cause readmission to hospital within 30 days (36)
23
24 388 and 60 days (37) of discharge, in older adults.

25 26 27 28 29 389 **Number of medications at admission ≥ 5**

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32 390 Polypharmacy is a commonly indicated risk factor for medication-related problems in older adults
33
34 391 (39). Polypharmacy, in itself, is not necessarily a bad thing but with age comes physiological changes
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36 392 that affect the pharmacokinetics and pharmacodynamics of medications. This leads to increased
37
38 393 sensitivity (39, 40) which, in turn, leads to an increased risk of medication-related problems (39). The
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40 394 presence of polypharmacy (32, 41, 42) and medication-related problems (8, 43) can lead to
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42 395 increased healthcare use and, as shown in this study, to possibly medication-related readmissions.
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44 396 Hence, polypharmacy was included in the HOME Score. Similarly, the number of medications used is
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46 397 included as a risk factor in the PRIME tool (16) as well as in the decision support tool predicting
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48 398 elderly patients' risk of readmission based on their high-risk medication regimens, developed by
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50 399 Olson et al (17).

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400 Emergency admission

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

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

412 Implications for clinical use

413 Healthcare involving multimorbid older adults is complex and integrating care across disciplines, as
414 well as working together in interdisciplinary teams, is important to achieve safe and effective
415 healthcare (11, 12, 14, 44). Improving medication use as well as transitions of care has been shown
416 to be important factors when aiming to reduce the frequency of medication-related readmissions
417 (11, 12). Including clinical pharmacists in the interdisciplinary team, to help with medication
418 reconciliation and medication review as well as information transfer and follow-up regarding
419 medications and medication changes, can support this (12, 45-47). The HOME Score can be used to
420 find the patients in most need of this support.

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

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3 424 related readmission, 90% of patients in the development cohort and 96% in the validation cohort
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5 425 were indeed not readmitted due to medication-related problems. Hence, using the HOME Score,
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7 426 healthcare personnel can easily rule out 50% of patients 65 years and older who are not at increased
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9 427 risk of medication-related readmission. This can be done already at admission to hospital, and in
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11 428 doing so, the efficiency and effectiveness of preventive actions aiming to improve medication use
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13 429 and transitions of care can probably improve. This can possibly, in turn, lead to an increase in patient
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15 430 safety as well as benefits to the health economy. Further studies are needed to test these
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17 431 hypotheses.
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22 432 **Strengths and limitations**

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25 433 According to the TRIPOD statement (15) an internal validation should always be performed when
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27 434 developing a prediction model, which was not done in this study. This choice was based on the fact
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29 435 that an external validation, using a geographically separate population, was performed. We
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31 436 considered this to be sufficient as clinical prediction models are always in need of further validation
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33 437 studies, as performance differs between locations, settings, and over time (48). Hence, this is just a
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35 438 first edition of the HOME Score and further studies are needed to test its clinical usefulness and to
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37 439 keep it up-to-date.
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41 440 The HOME Score was developed using data from a retrospective study performed in a population
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43 441 admitted to a single Swedish hospital. This could limit its generalisability, which is why an external
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45 442 validation was carried out using data from four other hospitals in another part of Sweden. The tool's
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47 443 predictive ability was withstanding, suggesting that it can be used when aiming to identify patients
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49 444 at increased risk of possibly medication-related readmission in Sweden. However, further studies are
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51 445 needed to assess the international validity of the HOME Score as well as its validity in other
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53 446 populations within Sweden. As stated previously, this is merely a first edition of the HOME Score and
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55 447 further studies are needed to test its clinical usefulness and to keep it updated.
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3 448 We chose to include the categorical variable *Number of medications at admission* ≥ 5 in the final risk
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5 449 score even though the mean number of medications was 10.30 in patients with a possibly
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7 450 medication-related readmission and 8.09 in the comparison group. This choice was based on the
8
9
10 451 Swedish directives and general advice (20) stating that a medication reconciliation should be
11
12 452 performed in admitted patients taking 5 medications or more, but it may have weakened the
13
14 453 prediction model. This is one of the aspects that should be examined when further validating the
15
16 454 HOME Score and investigating its clinical usefulness.

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20 455 The population used in developing the HOME Score was tailored for the identification of risk factors
21
22 456 for all-cause readmission and possibly medication-related readmission (10, 22). This led to a larger
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24 457 proportion of readmitted patients in the development cohort (50%) compared to the proportion in
25
26 458 the validation cohort (15%), the proportion of 30-day readmissions in the validation cohort being
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28 459 closer to that reported in previous studies (1-3). This could be considered a weakness.

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32 460 The tool AT-HARM10 (23) was used by clinical pharmacists in both the development (10) and
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34 461 validation cohort (25, 26) in order to assess whether 30-day readmissions were possibly or unlikely
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36 462 medication-related. This is a strength as the same definition of medication-related readmission was
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38 463 used in both populations. However, even though the tool has been validated (23), the assessments
39
40 464 are implicit, and the result depends on the person conducting them. This could be considered a
41
42 465 weakness. The fact that the amount of possibly medication-related readmissions was almost the
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44 466 same in the development and validation cohort (40% in the development cohort and 41% in the
45
46 467 validation cohort) indicates that this may not be a big issue.

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51 468 In the development cohort, included patients were admitted to medical as well as surgical
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53 469 departments whereas patients in the validation cohort were admitted solely to medical wards. This
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55 470 could have affected the results and further validations of the HOME Score are needed in order to
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57 471 establish its clinical usefulness in different departments as well as in other countries.
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67 473 **CONCLUSION**

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10 474 The HOME Score can be used to identify older adults at increased risk of possibly medication-related
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12 475 readmission within 30 days of discharge. The tool is easy to use and includes variables that should be
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14 476 readily available in electronic health records at admission, thus making it possible to implement risk-
15
16 477 reducing activities during the hospital stay as well as at discharge and in transitions of care. These
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18 478 activities could possibly help increase patient safety as well as be beneficial to the health economy
19
20 479 but further studies are needed to investigate the clinical usefulness of the HOME Score as well as the
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22 480 benefits of implemented activities.
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26 481
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2930 482 **ACKNOWLEDGEMENTS**

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32
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38
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40
41 487 and Health (SWEAH).
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4950 489 **STATEMENTS**51
52
53 490 **Competing interests**

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55
56 491 The authors declare that they have no competing interests.
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492 **Author contributions**

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

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502 or in writing the manuscript.

503 **Ethics statement**

504 Ethical approval was applied for and approved by the Swedish Ethics Review Authority (Dnr 2021-
505 06612-01).

506 **Data Availability Statement**

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

512

513 FIGURE LEGEND

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

519 SUPPORTING INFORMATION

520 **Appendix 1. Assessment Tool for identifying Hospital Admissions Related to Medicine (AT-
521 HARM10).** Includes the AT-HARM10 assessment tool, instructions for use and representative
522 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		
<i>A score of 4 or more denotes increased risk</i>		

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

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

5
6 Yes → P

7
8 No → NQ

9 **NOTE:** An admission caused by side effects of appropriate medication treatment should be
10 classified as *possibly* medication-related.
11
12
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- 14 6. Are there abnormal laboratory results or vital signs that could be *medication-related* and might
15 have caused the admission?

16
17 Yes → P

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

24
25 Yes → P

26
27 No → NQ
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- 30 8. Did the patient have any *previously* diagnosed untreated or suboptimally treated (e.g. dose too
31 low) indications that might have caused the admission?

32
33 Yes → P

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

40
41 Yes → P

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43 No → NQ
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- 46 10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?

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48 Yes → P

49 No → P (the tool has not been able to rule out that the admission is medication-related)
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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.

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

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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.

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

5
6 **Yes:** A patient with dementia, who has recently been prescribed an anticholinergic medication
7 (e.g. hydroxyzine), admitted with confusion.
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11 8. Did the patient have any, *previously* diagnosed, untreated or suboptimally treated (e.g. dose too
12 low) indications that might have caused the admission?
13

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

16 **Yes:** A patient admitted because of a hip fracture who had a prior diagnosis of osteoporosis but
17 was not taking osteoporosis prophylaxis.
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22 9. Was the patient admitted because of a problem with the dosage form or pharmaceutical
23 formulation (i.e. failure to receive the medication)?
24

25 **Yes:** A patient admitted with worsening asthma who was found to be unable to use the inhalers
26 correctly.
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28 **Yes:** A patient admitted with palpitations who was found to be unable to swallow tablets and
29 had been crushing slow-release antihypertensive tablets that should have been swallowed whole
30 to retain their slow-release effects.
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35 10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?
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37 **Yes:** A patient whose prednisolone treatment has been discontinued too abruptly admitted with
38 nausea, vomiting and diarrhoea.
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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 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

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2 *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
3 denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD
4 Explanation and Elaboration document.
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