PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Glans, Maria; Kempen, Thomas; Jakobsson, Ulf; Kragh Ekstam, Annika; Bondesson, Åsa; Midlöv, Patrik

VERSION 1 – REVIEW

REVIEWER	Danielle R Fixen University of Colorado
REVIEW RETURNED	27-Jan-2023

GENERAL COMMENTS	Well written and laid out analysis of readmissions. However, I felt the title is misleading and the tool you developed cannot specifically say that readmissions are due to medications. The tool weighs ED visits higher and has other factors that play a role into readmission. Would recommend taking out "medication related" from the title.

REVIEWER	Justin Cousins University of Tasmania, School of Pharmacy and Pharmacology
REVIEW RETURNED	16-Feb-2023

GENERAL COMMENTS	An interesting and worthwhile topic with a clear objective and sensitivity and specificity of the tool similar to other medication-related harm tools. Possibly-medication-related admissions seems high at 40%. Providing further detail in the results on the participants characteristics including age, comorbidities, medication implicated etc would be beneficial for the reader to gain context. Providing the detail to the statement " a relatively large proportion of readmissions are medication related" would help put the results of this paper in context. Likewise discussing the heterogeneity in definitions utilised that may lead to the differences. Further discussion on the different elements with Parekh's PRIME tool would add context to the discussion and clarify the HOME tools potential role, noting the exclusion of "possible" medication-related harm in Parekh's tool. Could the inclusion of possible problems be considered a limitation? Context provided on Swedish regulations and adherence in the methods may be better placed in the introduction? Is regulation the correct word, or are they guidelines/general advice? The reference (18) supporting the statement on increasing patient

	safety and reallocation of resources seems out of context without understanding the medication harm found in your study. Detail on the nature of problems identified as noted above would help inform how the tool could be utilised, linking to the above statement in the introduction. Is most of the harm related to cardiovascular medication hence the cardiology reference to improve safety and allocate resources?

REVIEWER	Anne-Laure Blanc Hopitaux Universitaires de Geneve, Pharmacy
REVIEW RETURNED	12-Apr-2023

GENERAL COMMENTS	Dear Authors, Thank you for submitting this interesting and clearly structured study. The manuscript is well written and easy to read. This topic is important, however after reading this manuscript, I wonder how many patients the HOME score will identify as “at high risk of medication related readmission”, and how healthcare team would deal with this. The variable included in the score are common among older hospitalised patients. This score seams to perform better for identifying patient that will not be at risk of medication related readmission base on PPV and NPV. Please comment on this in the discussion section of the manuscript. Irrespectively of this, I found this study and the development of this score worthy of interest. Here under you will find some concerns: 1) Abstract section : a. please specify in the abstract method section how was the “medication related readmissions” defined. b. In the result section, the C-index, in my opinion, can not be defined as “good” (usually a C-Index > 0.7 indicate a good model, > 0.8 a strong model, and a value of 0.5 a model no better than predicting an outcome than random chance). Please qualify the calibration performance (i.e “quite good” or “fairly good”). 2) Method section : a. Please specify how was defined the 30 days readmission (in any department of hospital? Including emergency consultation? Only hospitalisation? Preventable 30 day readmission? …). b. Why not having involved variable on medication other than the number of medication? Drug class (anticoagulant? Anti-diabetes…) ? High-risk drugs? Please comment. c. Why not having done an internal validation before the external validation? Please add this information in the manuscript. 3) Results section: a. Please justify in more detail the use of hospitalisation in the last 12 month as a binary predictor? Why not the hospitalization in the last 6 months like in the LACE index? b. Please justify in more detail the use of medication at admission>5 as a binary predictor ? why “only 5 medications” (lots of hospitalized elderly patients receive more than 5 medications) ? polymedication is a risk factors of hospital readmission indeed but the precise

	numbers associated with readmission remains uncertain. c. Please add a table with the patient distribution regarding the point obtained with the Home score in the derivation and validation cohort, including the observed and predicted risk. This is an interesting result when thinking of the possible use of your score . Points Patient distribution (nb/%) Observed risk (%) Predicted risk (%) Derivation cohort < 4 points > 4 points Validation cohort < 4 points > 4 points 4) Discussion section : a. Once again, I am not sure you can say that your score perfom "good". Please nuance this result in the first paragraph of the discussion section (line 277 + 278). b. When available the patient distribution of high risk of medication readmission (Home score > 4), please discuss in more details the implementation of risk reduction activities (line 279-280) in order to contextualize the use of HOME score. c. Please comment your last result in the external validation: "the number of correctly predicted patients was 23 (out of 54)", line 270-271. This mean a 50% of correctly predicted patient. d. HOSPITAL Score and LACE Index score are mentioned in this discussion section. The PAR-Risk Score (1), also focus on potentially avoidable readmission (as the HOSPITAL score) can be mentioned as an other score focused on hospital readmissions. The difference between hospital readmission definition can also be discussed, as well as the variable included. e. In the paragraph "implications for clinical use", please add examples of activities that can be implemented (line 366-367), focusing on medications and therefore justifying the development of a specific score on medication related readmission (and not all cause of hospital readmission). f. Line 367 "the Home Score could likely help increase the efficiency and effectiveness of such interventions". This need to be tested in a specific prospective study. Please moderate this statement. g. Line 368 "this, in turn, could lead to an increase in patient safety as well as benefits to the health economy". Again, this need to be tested in a specific prospective study. Please moderate this statement. h. Limitation: paragraph focus on the AT-HARM10 to identify medication related readmission: This tool was used by clinical pharmacists. Would the identification of medication related readmission be different if it was used by a nurse or a medical doctors? And what would it change the variable included? Please add some comments on this. Also add more details on the validation of the AT-HARM10 in this

	section. It seems to be internally validated in one study, with an identification of 50% of the medication related admission. “Both AT-HARM10 and the gold standard identified approximately 50% of the admissions as MRAs” (ref : Kempen, T.G.H., Hedström, M., Olsson, H. et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm 41, 198–206 (2019)). Please justify the choice of this tool in the method section, and mentioned these limitations in the discussion paragraph dedicated to the limitations. Reference : 1) Blanc AL, Fumeaux T, Stirnemann J, Dupuis Lozeron E, Ourhamoune A, Desmeules J, Chopard P, Perrier A, Schaad N, Bonnabry P. Development of a predictive score for potentially avoidable hospital readmissions for general internal medicine patients. PLoS One. 2019 Jul 15;14(7):e0219348.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Danielle R Fixen, University of Colorado
Comments to the Author:

- Well written and laid out analysis of readmissions. However, I felt the title is misleading and the tool you developed cannot specifically say that readmissions are due to medications. The tool weighs ED visits higher and has other factors that play a role into readmission. Would recommend taking out "medication related" from the title.

Response: Thank you for your comment which is, of course, valid considering the variables included in the HOME Score.
However, since the tool is in fact developed by comparing patients with a possibly medication-related readmission to those not readmitted as well as those readmitted to other causes than medications, we respectfully disagree and have decided to maintain the use of “medication-related” in the title.

Reviewer: 2
Mr. Justin Cousins, University of Tasmania
Comments to the Author:

- An interesting and worthwhile topic with a clear objective and sensitivity and specificity of the tool similar to other medication-related harm tools.
Possibly-medication-related admissions seems high at 40%.

Response: A valid comment considering previous literature on the subject. However, when using the Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10), possibly medication-related readmissions are defined as admissions due to medication related problems (MRPs) as defined by Strand (1), i.e. an “undesirable patient experience that involves medication therapy and that actually or potentially interferes with desired patient outcomes”. This means that medication-related problems involve not only adverse drug reactions but also problems such as inappropriate prescribing, non-compliance, and problems related to over-the-counter medications (2). This has now been further described in the Methods section under the headline Study sample and procedure, starting at line 147.

With this we mean that the definition of medication-related readmission is broader than in many other studies which may be the reason for the 40%. As shown in the study, the proportion of medication-related readmission in the development cohort was almost exactly the same as in the validation

cohort, in which AT-HARM10 was also used – suggesting that the proportion is plausible, when using this tool. The use of the same tool in the development cohort and the validation cohort is a strength now described in the Discussion section under the headline Strengths and limitations starting at line 459.

- Providing further detail in the results on the participants characteristics including age, comorbidities, medication implicated etc would be beneficial for the reader to gain context.

Response: Indeed, yes, but in this case we must respectfully refer to the studies from which data was taken to gain this context - in order to maintain focus on the development and validation of the risk assessment tool. We have therefore added the words “the population” to the sentence starting on line 135 – where we refer to our own studies (3, 4) for further information on the development cohort. Similarly, we now refer to Kempen et al (5) for further information on the population and methods used in the MedBridge trial – see line 205-206.

- Providing the detail to the statement “a relatively large proportion of readmissions are medication related” would help put the results of this paper in context. Likewise discussing the heterogeneity in definitions utilised that may lead to the differences.

Response: Thank you. We have added some more details regarding the proportion of readmissions related to medications and why they differ between studies, in the Introduction section starting at line 79.

- Further discussion on the different elements with Parekh’s PRIME tool would add context to the discussion and clarify the HOME tools potential role.

Response: Thank you. We have now added some further details on the definition of medication-related readmissions as assessed using AT-HARM10 - in the Methods section under the headline Study sample and procedure, starting at line 150.

We have also added some further information on the type of medication-related health care predicted by the PRIME tool as well as the differences in definition of “medication-related” between the PRIME tool and the HOME Score – in the Discussion section under the headline Comparisons to other studies, starting at line 337.

- Noting the exclusion of "possible" medication-related harm in Parekh’s tool. Could the inclusion of possible problems be considered a limitation?

Response: Thank you for an insightful comment. Indeed, with AT-HARM10 only possibly, and not certain, medication-related readmissions are identified which could, perhaps, be considered a limitation. However, we find that as the purpose of the HOME Score is to find patients in which to implement interventions aiming to reduce the risk of medication-related readmission, we would rather have an increased sensitivity, so as to not miss too many patients at risk. Therefore, we find the broader definition of medication-related readmissions used in AT-HARM10 and the HOME Score to be satisfactory. We have respectfully decided not to add these thoughts to the Discussion.

- Context provided on Swedish regulations and adherence in the methods may be better placed in the introduction? Is regulation the correct word, or are they guidelines/general advice?

Response: Thank you, it is called “directives and general advice”, not regulations, and we have changed the wording accordingly. However, we find that the section should remain in the Methods section, under the headline Settings, as it gives context to the term “usual care”.

- The reference (18) supporting the statement on increasing patient safety and reallocation of resources seems out of context without understanding the medication harm found in your study. Detail on the nature of problems identified as noted above would help inform how the tool could be utilised, linking to the above statement in the introduction. Is most of the harm related to cardiovascular medication hence the cardiology reference to improve safety and allocate resources?

Response: We agree, this is out of context, and the reference has been removed. Instead, we have simply stated that using a risk assessment tool developed for the purpose of identifying patients at increased risk of medication-related readmission could make it possible to not only increase patient safety but also relocate some resources to other areas within healthcare.

Reviewer: 3
Miss Anne-Laure Blanc, Hopitaux Universitaires de Geneve, Hôpitaux de l'Est Lémanique (PHEL)
Comments to the Author:
Dear Authors,

- Thank you for submitting this interesting and clearly structured study. The manuscript is well written and easy to read.
This topic is important, however after reading this manuscript, I wonder how many patients the HOME score will identify as "at high risk of medication related readmission", and how healthcare team would deal with this. The variable included in the score are common among older hospitalised patients. This score seams to perform better for identifying patient that will not be at risk of medication related readmission base on PPV and NPV. Please comment on this in the discussion section of the manuscript.

Response: Thank you for this insightful comment. We have commented on this in the Discussion section under the headline Implications for clinical use starting at line 420.

- Irrespectively of this, I found this study and the development of this score worthy of interest.
Here under you will find some concerns:
1) Abstract section:
a. please specify in the abstract method section how was the "medication related readmissions" defined.

Response: Unfortunately, we find that this information is not possible to fit into the Abstract due to the maximum word limit. We have, however, included further information on AT-HARM10 and the definition used for medication-related (re)-admissions using this tool - in the Methods section under the headline Study sample and procedure starting at line 150.

b. In the result section, the C-index, in my opinion, can not be defined as "good" (usually a C-Index > 0.7 indicate a good model, > 0.8 a strong model, and a value of 0.5 a model no better than predicting an outcome than random chance). Please qualify the calibration performance (i.e "quite good" or "fairly good").

Response: Thank you, a valid point. Due to word restrictions, again, we have actually stricken the sentence in the Abstract stating that calibration was good and simply reported the c-indexes.

2) Method section:
a. Please specify how was defined the 30 days readmission (in any department of hospital? Including emergency consultation? Only hospitalisation? Preventable 30 day readmission? …).

Response: This is indeed important information, and it has now been clarified that patients in the study group were readmitted to hospital for at least 24 hours and that they were admitted to any department - in the Methods section, under the headline Study sample and procedure, starting at line 143.

b. Why not having involved variable on medication other than the number of medication? Drug class (anticoagulant? Anti-diabetes…)? High-risk drugs? Please comment.

Response: Thank you, this is a valid query as we are looking at medication-related readmission.
It is very possible that the HOME Score could benefit from adding variables such as specific medications or diagnoses in order to make it more specific. However, this was not done in this study simply because we based the development of the risk score on the results of our previous study (4) where specific medications were not included. Also, we wanted to include only variables known already at admission in the risk score and we argue that the medications potentially causing a readmission cannot be known until discharge – hence, they cannot be included in the risk score.

However, as further stated in the Discussion section under the headline Strengths and limitations, this is a “first edition” of the HOME Score and further studies are needed to test its clinical usefulness and to keep it updated.

c. Why not having done an internal validation before the external validation? Please add this information in the manuscript.

Response: Indeed, it is stated in the TRIPOD statement that an Internal validation should be performed and our choice not to do this has now been commented on in the Discussion section under the headline Strengths and limitations starting at line 432.

3) Results section:
a. Please justify in more detail the use of hospitalisation in the last 12 month as a binary predictor? Why not the hospitalization in the last 6 months like in the LACE index?

Response: Thank you for your comment. This is a choice we made in our first study where we looked at all-cause readmission to hospital within 30 days of discharge (3). In this study we included both the variable Admissions to hospital within the last 12 months, which is a variable included in the HOSPITAL Score (6) and Number of ED visits within the last 6 months which is included in the LACE index (7). Since our interest was admissions to hospital and not “merely” ED visits we chose to include the variable looking at hospital admissions in the prediction model.

The reason for making the variable binary was simplicity – we wanted the risk score to be as simple to use as possible.
How we ended up defining the categorical variable has now been further described in the Results section under the headline Variables included, starting at line 239.

b. Please justify in more detail the use of medication at admission>5 as a binary predictor? why “only 5 medications” (lots of hospitalized elderly patients receive more than 5 medications) ? polymedication is a risk factors of hospital readmission indeed but the precise numbers associated with readmission remains uncertain.

Response: Thank you, we agree that lots of elderly patients receive more than five medications, however, again, we strived for simplicity and therefor chose to use a binary variable.

As to why we chose this exact number of medications in the risk score – this has now been further described in the Results section under the headline Variables included, starting at line 243.

c. Please add a table with the patient distribution regarding the point obtained with the Home score in the derivation and validation cohort, including the observed and predicted risk. This is an interesting result when thinking of the possible use of your score.
Points Patient distribution (nb/%) Observed risk (%) Predicted risk (%)
Derivation cohort
< 4 points
> 4 points
Validation cohort
< 4 points
> 4 points

Response: Thank you for this comment, Table 3 has now been revised.

4) Discussion section:
a. Once again, I am not sure you can say that your score perfom “good”. Please nuance this result in the first paragraph of the discussion section (line 277 + 278).

Response: Thank you, we agree and have amended this – lines 314 and 315.

b. When available the patient distribution of high risk of medication readmission (Home score > 4), please discuss in more details the implementation of risk reduction activities (line 279-280) in order to contextualize the use of HOME score.

Response: We have added information on the distribution in Table 3 and the implementation of risk reducing activities is now further discussed in the Discussion section under the headline Implications for clinical use.

c. Please comment your last result in the external validation: “the number of correctly predicted patients was 23 (out of 54)”, line 270-271. This mean a 50% of correctly predicted patient.

Response: Yes, 50% of patients were correctly predicted. This is now further commented on in the Discussion section under the headline Implications for clinical use.

d. HOSPITAL Score and LACE Index score are mentioned in this discussion section. The PAR-Risk Score (1), also focus on potentially avoidable readmission (as the HOSPITAL score) can be mentioned as another score focused on hospital readmissions. The difference between hospital readmission definition can also be discussed, as well as the variable included.

Response: Thank you and apologies for overlooking this study. We have included the PAR-Risk Score in the Discussion section under the headline Comparisons to other studies, line 324, as well as under the headline Hospitalisations within the last 12 months ≥2, line 367. However, as the PAR-Risk Score is not aiming to identify patients at increased risk of medication-related readmissions we have not discussed it in great detail.

e. In the paragraph “implications for clinical use”, please add examples of activities that can be implemented (line 366-367), focusing on medications and therefore justifying the development of a specific score on medication related readmission (and not all cause of hospital readmission).

Response: Thank you, this has been done, starting at line 416.

f. Line 367 “the Home Score could likely help increase the efficiency and effectiveness of such interventions”. This need to be tested in a specific prospective study. Please moderate this statement.

Response: We hope that it is now clear that we agree that further studies are needed.

g. Line 368 “this, in turn, could lead to an increase in patient safety as well as benefits to the health economy”. Again, this need to be tested in a specific prospective study. Please moderate this statement.

Response: We agree that further studies are needed in order to verify our theories and have, we hope, sufficiently pointed this out.

h. Limitation: paragraph focus on the AT-HARM10 to identify medication related readmission: This tool was used by clinical pharmacists. Would the identification of medication related readmission be different if it was used by a nurse or a medical doctors? And what would it change the variable included? Please add some comments on this.
Also add more details on the validation of the AT-HARM10 in this section. It seems to be internally validated in one study, with an identification of 50% of the medication related admission. “Both AT-HARM10 and the gold standard identified approximately 50% of the admissions as MRAs” (ref : Kempen, T.G.H., Hedström, M., Olsson, H. et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm 41, 198–206 (2019)). Please justify the choice of this tool in the method section, and mentioned these limitations in the discussion paragraph dedicated to the limitations.

Response: Indeed, AT-HARM10 was used by a clinical pharmacist in our study, and it was developed with this group (clinical pharmacists) in mind. However, in the study where AT-HARM10 was developed and validated (2) the admissions identified as possibly medication-related by the clinical pharmacists using AT-HARM10 were similar to those identified by “the gold standard” which, in this study, included a consultant physician and a senior clinical pharmacist. Both groups identified 50% of the admissions as possibly medication-related. Based on this we believe that if AT-HARM10 was used by a nurse or medical doctor instead of a clinical pharmacist the result would probably be the same. However, as this has not been tested, we cannot be certain.

We have, respectfully, decided not to add more information regarding this issue in the Discussion section under the headline Strengths and limitations as we have already stated that the assessments are implicit and depend on the person conducting them. The strength here is that we do, indeed, use the same definition of medication-related (re)admission in the development cohort and in the validation cohort which is quite uncommon in studies regarding this issue. This is discussed in the Discussion section under the headline Strengths and limitations, starting at line 459.

We have added some further information on AT-HARM10, further describing the type of medication-related problems identified by the tool - in the Methods section, under the headline Study sample and procedure, starting at line 150. We hope this makes it easier to compare it to other tools such as the PRIME tool (8). We have also included some information regarding this issue in the Discussion section under the headlines Comparison to other studies (starting at line 337) and Implications for clinical use (starting at line 420).