A tool for prediction of risk of rehospitalisation and mortality in the hospitalised elderly: secondary analysis of clinical trial data

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ABSTRACT

Objectives: To construct and internally validate a risk score, the ‘80+ score’, for revisits to hospital and mortality for older patients, incorporating aspects of pharmacotherapy. Our secondary aim was to compare the discriminatory ability of the score with that of three validated tools for measuring inappropriate prescribing: Screening Tool of Older Person’s Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI).

Setting: Two acute internal medicine wards at Uppsala University hospital. Patient data were used from a randomised controlled trial investigating the effects of a comprehensive clinical pharmacist intervention.

Participants: Data from 368 patients, aged 80 years and older, admitted to one of the study wards.

Primary outcome measure: Time to rehospitalisation or death during the year after discharge from hospital. Candidate variables were selected among a large number of clinical and drug-specific variables. After a selection process, a score for risk estimation was constructed. The 80+ score was internally validated, and the discriminatory ability of the score and of STOPP, START and MAI was assessed using C-statistics.

Results: Seven variables were selected. Impaired renal function, pulmonary disease, malignant disease, living in a nursing home, being prescribed an opioid or being prescribed a drug for peptic ulcer or gastroesophageal reflux disease were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked to a lower risk of the outcome. These variables made up the components of the 80+ score. The C-statistics were 0.71 (80+), 0.57 (STOPP), 0.54 (START) and 0.63 (MAI).

Conclusions: We developed and internally validated a score for prediction of risk of rehospitalisation and mortality in hospitalised older people. The score discriminated risk better than available tools for inappropriate prescribing. Pending external validation, this score can aid in clinical identification of high-risk patients and targeting of interventions.

Strengths and limitations of this study

- The 80+ score is based on data from a population on which there are strong incentives to focus: patients at high risk of hospitalisation and also of mortality.
- The score is constructed from a prediction model that includes aspects of pharmacotherapy. The use of drugs can be either positively or negatively causally related to a clinical outcome, and can also be important indicators for a certain condition, disease or circumstance.
- Data from a limited number of patients being admitted to an acute internal medicine ward at one hospital only were used in the construction of the score. The generalisability of the score is therefore unknown.
- The 80+ score was internally validated, but external validation is required before general use and recommendation.

BACKGROUND

Hospitalisations of older people pose an increasing economic burden on healthcare systems in the developed world. During recent years, attempts have been made to identify risk factors for hospital readmissions in order to help target interventions and decrease readmission rates.1 2 Variables tested for their ability to predict readmissions have included patient demographic factors, medical comorbidity data, laboratory data, social determinants of health, patient functional status and prior use of healthcare services. However, the patients’ medication use has rarely been evaluated as potential predictors of readmissions. As adverse drug reactions are the main cause of up to a fourth of hospital admissions3-5 and are ranked as the fourth to sixth leading cause of death in the USA,6 this is surprising. In older people, multiple coexisting diagnoses and concomitant
multidrug use are common. This group is also, due to pharmacokinetic and pharmacodynamic changes, at increased risk of adverse drug reactions and, hence, hospitalisations and mortality. For this population in particular, the use of medications should be considered as a potential prognostic factor for revisits to hospital and mortality.

There are several tools available for assessment of appropriateness of prescribing in older people, which can be used prospectively as guides to appropriate prescribing or retrospectively for evaluation of the quality of prescribing. The tools are either checklist-based or judgement-based. Examples of checklist-based tools are STOPP (Screening Tool of Older Person’s Prescriptions), identifying drugs that should be avoided in certain situations, and START (Screening Tool to Alert doctors to Right Treatment), identifying irrational prescribing omissions. Medication Appropriateness Index (MAI) is a validated judgement-based tool and includes 10 aspects of appropriateness of prescribing: indication, effectiveness, dosage, correct and practical directions, drug–drug and drug–disease interactions, duplication, duration and costs. These tools have mainly been developed through literature search and expert opinion. However, the association between inappropriate medication use in older people and poor health outcomes still remains uncertain. The evidence for a link between the tools and clinical outcomes is not convincing for any of them.

In Sweden, as an attempt to improve the quality of prescribing and reduce drug-related morbidity, a number of drugs and drug classes have been recognised as inappropriate to elderly people (Swedish Association of Local Authorities and Regions (SALAR) drugs) and there is a national initiative aiming to reduce the prescribing of these drugs with economic reimbursement as incentives. The association between the prescribing of these drugs and negative clinical outcome has not been investigated.

The aim of this study was to construct a tool for estimating risk of revisits to hospital or mortality for older people, incorporating aspects of pharmacotherapy. The secondary aim was to compare the discriminatory ability of this tool, or score, with three validated tools for appropriate prescribing: STOPP, START and MAI and with the SALAR drug list.

**METHODS**

**Study participants and data**

Patient data from a prospective randomised controlled trial (RCT) were used. The main objective of the RCT was to study the effects of adding a ward-based pharmacist service to the healthcare team on clinical outcomes (number of rehospitalisations; readmissions or emergency department visits) for elderly patients. Four hundred patients, aged 80 years and older and acutely admitted to the internal medicine wards at Uppsala University Hospital, were included and randomised in the control or intervention group. The patients in the intervention group received an enhanced pharmacist service during the hospital admission. All patients were followed for 12 months after hospital discharge, and the number of and time for revisits to hospital and/or mortality was recorded. Each participant gave written informed consent. In this study, the group assignment was not taken into consideration in the analyses.

**Outcome variables**

A composite variable (combining the event of an unplanned rehospitalisation (emergency department visit or readmission) or death during the 12-month follow-up period) was chosen as the end point for the analysis. The outcome variable in the regression analysis and the goodness-of-fit analysis was the time to the end point from the day of discharge from index admission. The outcome variable in the assessment of discriminatory ability was the occurrence of an event (ie, the end point).

**Statistical analyses**

**Identification of risk factors**

Candidate variables were selected based on a combination of clinical judgement and statistical properties of the variables. Clinical and drug variables were included. The selected clinical variables were: gender, age, renal function (estimated glomerular filtration rate (eGFR)), level of social support and medical history (heart failure, diabetes mellitus, pulmonary disease (chronic obstructive pulmonary disease (COPD) or asthma), arrhythmia, malignant disease (past or present), coronary artery disease, cerebral vascular lesion (past), myocardial infarction (past), hypertension and dementia). The drug variables were the patients’ prescribed medications, categorised into groups based on the Anatomical Therapeutic Chemical (ATC) classification system and on similar effect and risk in elderly people or categorised according to the SALAR drug list (SALAR drug list presented in table 1). In case a SALAR drug variable was the same as an ATC-based category variable, one of them was excluded. The drug variables were also potentially inappropriate medications (identified by STOPP) and potential prescription omissions (identified by START). Variables with less than 10 patients in the smallest group were excluded from further analyses. In order to detect potential redundancies among the variables, a principal component analysis (PCA) was performed. If two variables were collinear, the variable with the most balanced categories were included for further study. The remaining clinical, drug-disease and drug variables were then subject to a backward stepwise Cox regression likelihood-ratio elimination procedure. To minimise type I errors, the p value limit for inclusion was set to 0.01. The set of variables extracted from this analysis, that is, the risk factors, makes up the components of our new score.

**Development of point score system**

We developed a point score system for risk estimation, the ‘80+ score’, following the Framingham Heart Study approach. First, the continuous independent variable,
eGFR, was organised into categories representing different levels of renal function. Reference values were determined for each of these categories. The remaining independent variables were modelled by sets of dichotomous indicator variables. For each variable, a base category was determined (using their most prevalent category). We then calculated how far each category was from the base category by dividing the regression unit for the category by a constant (B) that was common to all variables. The resulting quotient was rounded to the nearest whole number, which was used as the points associated with that category. The point score system is the 80+ score. Last, the risk associated with each level of the score was calculated. For this last step, the following formula was used: risk estimate = \(1 - S_0(t) \exp(\Sigma \hat{\beta} x - \Sigma \hat{\beta}_\text{mean})\), where \(S_0(t)\) was the average 1-year event-free rate, and \(\Sigma \hat{\beta}_\text{mean}\) was the sum of the variables’ regression coefficients (\(\hat{\beta}\)) multiplied with the means or proportions of the variables in the sample (table 1). \(\Sigma \hat{\beta}_x\) was approximated from multiplying the constant for the model (B) with the point score and adding back the base value (ie, the reference value for the base category) for the continuous variable eGFR.

The goodness-of-fit of the 80+ score was assessed by the Grønnesby-Borgan test\(^{30}\) and calibration was assessed by plotting predicted risk versus observed risk. The discriminative ability of the 80+ score was assessed using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provides the probability of the model giving a higher predicted risk to the patient that will have an event than the one that will not. We internally validated the score using an enhanced bootstrap with 1000 iterations, in order to quantify and account for the extent of overoptimism in our prediction model.\(^{31}\) We present optimism-corrected C-statistics for the 80+ score.

The effect of the pharmacist intervention was not adjusted for in the regression analyses. The reason for this was that the intervention directly affected the results of the STOPP, START and MAI scores as well as the

| Table 1 | Data used for calculation of point score system |
|---------|-----------------------------------------------|
| **Proportion of patients in each category** | **\(W\) and \(W_{\text{ref}}\) for each category** | **Regression unit for each category** | **Point score** |
| eGFR* | 0.014 | 105 mL/min=\(W_{\text{ref}}\) | 0 |
| >90 mL/min | 0.128 | 74.5 mL/min | 0.397 | 1 |
| 60–89 mL/min | 0.552 | 54.5 mL/min | 0.787 | 2 |
| 30–59 mL/min | 0.307 | 17.5 mL/min | 1.138 | 3 |
| Social support | | | | |
| Living alone or with spouse | 0.818 | 0.481 | 0=W_{\text{ref}} | 0 |
| Nursing home | 0.182 | 1 | 0.481 | 0.481 |
| Pulmonary disease† | 0.878 | 0=W_{\text{ref}} | 0 | 0 |
| Yes | 0.122 | 1 | 0.481 | 0.724 |
| Malignant disease‡ | 0.834 | 0=W_{\text{ref}} | 0 | 0 |
| Yes | 0.166 | 1 | 0.506 | 0.506 |
| Prescription of drug for peptic ulcer and GERD | 0.674 | 0=W_{\text{ref}} | 0 | 0 |
| Yes | 0.326 | 1 | 0.362 | 0.724 |
| Prescription of opioid drug | 0.821 | 0=W_{\text{ref}} | 0 | 0 |
| Yes | 0.179 | 1 | 0.724 | 2 |
| Prescription of non-TCA-antidepressant drug | 0.791 | 0=W_{\text{ref}} | 0 | 0 |
| Yes | 0.209 | 1 | 0.506 | 0.506 |

The average 1-year event-free rate=0.3215§

Regression unit for each category=\(\hat{\beta}(W-W_{\text{ref}})\).

Point score=\(\hat{\beta}(W-W_{\text{ref}})/B\).

*Cockroft-Gault formula eGFR.

†Asthma or COPD.

‡Past or present.

§The Kaplan–Meier estimate of the event-free rate at the mean values of the risk factors.

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; TCA, tricyclic antidepressant.
frequency of prescribing of SALAR drugs and the overall number of drugs. As a sensitivity analysis, the C-statistic for the 80+ score was calculated for the control group patients only. The proportionality of hazards was assessed using Schoenfeld residuals and by inspecting cumulative incidence curves. We investigated the linearity of the association between eGFR and the outcomes by investigating models also including an ordinal variable for eGFR. Two-way interactions between the final set of variables in the score were investigated as deviations from multiplicativity. The score variables were also tested for the association with mortality only. All analyses were performed in IBM SPSS Statistics V21 and STATA V13.

RESULTS
Out of the 400 included and randomised patients in the RCT, 368 were evaluable for further analyses (27 patients died during the index admission and 5 patients wished to be excluded after the randomisation). Table 2 presents baseline characteristics for these patients. Two hundred and fifty (68%) patients had an event (ie, either a revisit to the hospital or death) during the 12 months follow-up period. In the group of patients that had an event, 212 (85%) were rehospitalised and the rest (15%) died.

Identification of risk factors
eTable 2A, B lists all variables taken into consideration in the analysis. Fourteen clinical variables and 64 drug variables met the inclusion criteria and were subject to the PCA. Three variables were excluded after the PCA: ‘B03B vitamin B12 and folic acid’ (collinear with STOPP h5; long-term opiates in patients with recurrent falls’), ‘G03C oestrogens’ and ‘R03AC drugs for obstructive airway diseases; selective β2-agonists’ (both collinear with R03B ‘drugs for obstructive airway diseases; anticholinergics + corticosteroids’).

Seventy-five variables were entered into the backward stepwise Cox regression. This procedure resulted in seven statistically significant variables, or risk factors, each having an individual association with the outcome variable. Four of the risk factors were clinical while three were drug-specific. Statistical information about the risk factors is presented in table 3. Past or present malignant disease and presence of pulmonary disease were both associated with an increased risk of rehospitalisation or mortality, as was impaired renal function. Further, living in a nursing home was linked to a higher risk of revisits to the hospital or death than living alone or with a spouse. Being prescribed a drug for peptic ulcer and gastroesophageal reflux disease (GERD) was associated with an increased risk (a vast majority of these prescriptions, 115 out of 120 (96%), were of a proton-pump inhibitor), as well as being prescribed a drug from the opioid class. Having an antidepressant drug (tricyclic antidepressants (TCAs) not included in this variable) was conversely associated with a lower risk.

Development of the point score system
Table 1 presents reference values (W and Wref) and regression units of each category of each risk factor variable—data that were used for development of point score. eGFR was organised into four levels of renal function. As reference values for these categories, the midpoints were chosen. For the other risk factor variables, the categories were assigned the value of 0 or 1. A referent risk factor profile was determined: a patient

| Baseline characteristics | All patients (n=368) |
|--------------------------|---------------------|
| Age, mean (SD), years    | 86.7 (4.1)          |
| Female, N (%)            | 216 (58.7)          |
| Body weight, mean (SD), kg| 61.3 (13.3)        |
| Laboratory values        |                     |
| eGFR*, mean (SD), mL/min/1.73 m² | 40.3 (18.5) |
| Haemoglobin level, mean (SD), mg/mL |            |
| Sodium level, N (%)      |                     |
| Hyponatraemia (<137 mEq/L) | 112 (30.4) |
| Within range (137–145 mEq/L) | 247 (67.1) |
| Hypernatraemia (>145 mEq/L) | 9 (2.4)           |
| Potassium level, N (%)   |                     |
| Hypokalaemia (<3.5 mEq/L) | 49 (13.3)          |
| Within range (3.5–5 mEq/L) | 295 (80.2) |
| Hyperkalaemia (>5 mEq/L) | 24 (6.5)           |
| Social support, N (%)    |                     |
| Living alone or with spouse | 301 (81.8) |
| Living in a nursing home | 67 (18.2)          |
| Medical history, N (%)   |                     |
| Heart failure            | 116 (31.5)          |
| Diabetes                 | 87 (23.6)           |
| Pulmonary disease (asthma or COPD) | 44 (12.0) |
| Arrhythmia               | 125 (34.0)          |
| Malignant disease (past and present) | 54 (14.7) |
| Coronary artery disease  | 114 (31.0)          |
| Cerebral vascular lesion (past) | 57 (15.5) |
| Myocardial infarct (past) | 87 (23.6)          |
| Hypertension             | 147 (39.9)          |
| Dementia                 | 47 (12.8)           |
| Annual incidence of rehospitalisations (95% CI) | 1.15 (1.01 to 1.32) |
| Annual incidence of mortality (95% CI) | 0.40 (0.33 to 0.48) |

*Cockroft-Gault formula eGFR.
COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.
with normal renal function, living alone or with a spouse, without diagnoses for pulmonary disease or malignant disease and with no prescription of drug for peptic ulcer or GERD, no prescription of opioids and no prescription of antidepressant drugs. The constant for the point score system (B) was selected, which was the regression coefficient for the variable ‘drugs for peptic ulcer and GERD’, 0.362. By dividing the regression unit for each category by B, it was computed how far the categories were from the base category. The point scores for each category for each risk factor variable were thus calculated. The point scores for the 80+ score system are presented in the right-hand column in table 1.

The point total is the summed score for each patient. For example, a patient with a renal function of 65 mL/min, living in a nursing home, diagnosed with COPD and prescribed a drug for peptic ulcer and GERD, would be given a point total of 1+1+2+1=5. The estimated risk associated with each point total in the 80+ score is shown in table 4. The estimated risk was computed using the formula described in the methods, where the \( \sum \beta x \) was calculated to –0.106842 and the \( \sum \beta x \) was approximated by multiplying B with the points and adding back the base value for eGFR (–0.012×105 mL/min). An example of risk estimation from the Cox regression as well as from the point score system is illustrated in the online supplementary material.

The goodness-of-fit of the 80+ score was good and is illustrated in figure 1. This was confirmed by the Grønnesby-Borgan test (p=0.49). A model including both an ordinal and a continuous variable for eGFR did not provide a better fit than a model with only the continuous variable (likelihood-ratio test p=0.11). There was some evidence of interactions between eGFR and the drug use variables ‘drugs for peptic ulcer and GERD’ and ‘non-TCA-antidepressants’, but the groups were very small. No deviations from proportionality were observed (all Schoenfeld’s test p>0.21).

When tested for their association with mortality only, the variables pulmonary disease, prescription of drug for peptic ulcer and GERD, and prescription of the non-TCA-antidepressant drug were not predictors of this

| Table 3 | Statistical information on 80+ score variables |
|---------|---------------------------------------------|
|         | Regression coefficient (SE) | Mean or proportion | p Value | HR  | 95% CI for HR |
| eGFR* (per mL/min/1.73 m²) | –0.012 (0.004) | 40.285 | 0.001 | 0.988 | 0.981 to 0.995 |
| Social support (living in nursing home vs living alone or with spouse) | 0.481 (0.162) | 0.182 | 0.003 | 1.617 | 1.176 to 2.224 |
| Pulmonary disease† (vs not) | 0.607 (0.177) | 0.122 | 0.001 | 1.834 | 1.296 to 2.595 |
| Malignant disease‡ (vs not) | 0.506 (0.166) | 0.166 | 0.002 | 1.659 | 1.198 to 2.297 |
| Prescription of drug for peptic ulcer and GERD (vs not) | 0.362 (0.135) | 0.326 | 0.008 | 1.436 | 1.101 to 1.872 |
| Prescription of opioid drug (vs not) | 0.724 (0.157) | 0.179 | 0.000 | 2.063 | 1.517 to 2.806 |
| Prescription of non-TCA-antidepressant drug (vs not) | –0.558 (0.170) | 0.209 | 0.001 | 0.573 | 0.410 to 0.799 |

Variables selected from backward stepwise Cox regression.
* Cockroft-Gault formula eGFR.
† Asthma or COPD.
‡ Past or present.

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; TCA, tricyclic antidepressant.

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Figure 1 Predicted risk versus observed risk for rehospitalisation or death.
outcome (p>0.05), while the link between social support and this outcome was strong (HR 3.107, 95% CI 2.081 to 4.640). The remaining variables showed similar predictive ability for the mortality outcome as they did for the combined outcome (rehospitalisation and mortality). Results are presented in etable 3.

A logistic regression model with the seven variables of the 80+ score as independent variables had a pseudo-$R^2$ of 0.13. The 80+ score demonstrated a satisfying discriminatory ability of the outcome, with a $C$-statistic of 0.715 (figure 2). The optimism was 0.001, rendering an optimism-corrected $C$-statistic of 0.714 for the 80+ score. This means that a patient with an event (revisit to the hospital or death) had a 71% probability of being given a higher risk score than a patient with no event. Figure 2 also shows that STOPP and START scores and the SALAR drug list were basically non-discriminating for the chosen outcome (with $C$-statistics just above 0.5). When tested in the control group only, the 80+ score had a $C$-statistic of 0.71, which is similar to the value for the group as a whole.

DISCUSSION

Using a clinical trial database of hospitalised patients, aged 80 years and above, the most relevant factors for identifying those at risk of an adverse outcome were identified. A simple scoring system intended for clinical use was constructed and internally validated, pending validation in an independent cohort. The score is suggested as a tool for identifying patients at highest risk of readmissions and mortality, and ultimately as an aid in clinical decision-making for improving outcomes in these patients. Increasing age, usage of medical services and poor health pose a risk of rehospitalisation and mortality, and hence there are strong incentives for focusing on this population.

Various risk factors for rehospitalisation and mortality have previously been identified in prediction models based on data from a variety of populations and settings, and with different candidate variables. The 80+ risk score has a higher discriminatory ability for risk of rehospitalisation and mortality than most other prediction models of today. This is most likely due to the fact that we included drug variables as candidate variables—the drugs can either be causally related to the outcomes or serve as important proxies for certain conditions, diseases or circumstances. Further, the precision was most likely maximised by developing the score using data from a narrowly defined population—these patients were all aged 80 years or older and had been acutely admitted to an internal medicine ward. In the majority of risk prediction models of today, rehospitalisation has been chosen as the outcome measure, but this carries a high risk of bias due to competing risk by death. Therefore, in this study, event-free (ie, no emergency department visit or readmission) survival was used as the end point.

The use of drugs deemed inappropriate has been associated with adverse drug events and it is often proposed that patients prescribed inappropriate medications should be prioritised for interventions—aimed at improving the quality of prescribing—in order to reduce the risk of unwanted clinical outcomes. However, in this set of patient data, neither the STOPP nor START tools had an ability to discriminate between patients at risk of rehospitalisation or mortality that was better than chance. The numbers of prescribed SALAR drugs showed similar results. MAI, being a judgement-based tool, has a moderate discriminatory ability for risk in this population. However, owing to its time-consuming nature, with assessment times per patient of up to 30 min, MAI is not suitable as a screening tool for patients in clinical practice. As has already been stated, none of the STOPP, START and MAI scores or the SALAR drug system are designed as risk scores. Still, the lack of consistent evidence for their association with clinical outcomes is notable and needs to be further investigated.

Pulmonary disease as well as impaired renal function are known risk factors for readmissions to hospital. These variables also emerged as risk factors in our population. Many nursing home residents have multiple morbidities and are high consumers of healthcare, which explains the prognostic ability of this variable. The unique finding in this study is that three drug variables were individually related to the clinical outcome in the multivariate model: being prescribed a drug for peptic
ulcer and GERD or being prescribed an opioid both appeared to increase the risk, while being prescribed an antidepressant drug was associated with a lower risk. The use of proton-pump inhibitors have in several studies been associated with various adverse events, such as Clostridium difficile infections and pneumonia, but another explanation for their association with the outcome variable is that the patients being prescribed these drugs have a history of ulcer (which was not among the candidate variables), which is a risk factor itself. This drug group may also function as a proxy for patients with multiple other comorbidities and polypharmacy since these patients have a potential need for preventive treatment for gastric disorders. Similarly, opioids can, as well as being a risk drug due to their potential to cause adverse drug reactions, be an indicator for pain or frailty (which are potential risk factors in themselves). The prescribing of non-TCA-antidepressants aims to provide relief from psychological symptoms and increase the patient’s general well-being, which supposedly has a protective effect on rehospitalisation and mortality. An alternative explanation for the negative association between this variable and the outcome is that these drugs may be given more often to physically healthier patients with a longer life expectancy. The rationale for exclusion of TCAs in the antidepressant variable is that the safety profile in elderly people for these drugs differs from that of the other antidepressants. TCA drugs were not a candidate variable in the analyses—since only five patients were prescribed these drugs—but were included in the ‘SALAR’ variable. The strong link between the level of social support and mortality is not surprising since patients often move to nursing homes for the last part of their lives. Interestingly, pulmonary disease or being prescribed a drug for peptic ulcer or GERD or a non-TCA-antidepressant drug was a predictor mainly for rehospitalisation.

A score for risk-identification purposes should have a satisfying predictive ability in the target population, and it should use data that are clinically readily available. The 80+ score meets these criteria. A simple and user-friendly point score system like this can quickly and easily identify high-risk patients. Yet, in order for this information to be useful, translation into suggested actions for reduction of this risk for these patients is crucial. This undertaking is obviously multifactorial. Nevertheless, by focusing on the patients with the highest risk, a pharmaceutical intervention, or other quality improvement effort, can be targeted more efficiently. For example, patients with COPD or asthma may benefit from a comprehensive patient education, and patients being prescribed an opioid or a drug for peptic ulcer or GERD may benefit from a thorough medication review.

The 80+ score was internally validated, but remains to be externally validated in another population before it can be generally recommended. A few limitations with this study need attention. Prior hospital visits have in several studies been associated with risk of rehospitalisation. This information was not available in this data set and has therefore not been included as a candidate variable. However, a potential weakness of having prior hospital visits as a variable in a clinical score is that this information may not be easily available on the patient’s admission to hospital. Another limitation is that the 80+ score is based on data from a limited number of patients being admitted to an acute internal medicine ward at one hospital only. This makes the generalisability unknown and increases the need for external validation. Finally, the limited sample size forced us to use the whole data set (both intervention and control group patients) for the development of the score. In this paper, we have discussed the role of prescribed drugs as potential risk factors for adverse clinical outcomes. However, it should be noted that the analyses do not take the potential risks of suboptimal use of drugs into consideration. Suboptimal drug use, such as patient non-adherence to treatment or lack of correct and complete transfer of information when patients are transitioned between different levels of healthcare, can cause adverse drug events and are risk factors of drug-related morbidity.

CONCLUSION

We have developed and internally validated a score intended for use in clinical practice to identify the hospitalised elderly patients at highest risk of rehospitalisation and mortality, accounting for pharmacotherapy. The score outperforms scores for inappropriate medication use in risk-prediction ability and can ultimately aid in clinical decision-making for improving outcomes in elderly patients.

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On-line only Supplemental Material

eTable 1. Swedish Associations of Local Authorities and Regions (SALAR) drug list

| Drug classes                                      | Example                                                      |
|--------------------------------------------------|--------------------------------------------------------------|
| Anticholinergic agents (SALAR a)                  | Alimemazine, hydroxyzine, prometazin, toterodine, tricyclic antidepressants |
| Long-acting benzodiazepine derivates (SALAR b)    | Diazepam, flunitrazepam, nitrazepam                          |
| Neuroleptics (SALAR n)                           | Haloperidol, olanzapine, quetiapine risperidone              |
| Oral nonsteroidal anti-inflammatory drugs (NSAIDs) (SALAR s) | Diclofenac, ibuprofen, naproxen                              |
| Tradolan (SALAR t)                               | Tramadol                                                     |
| Propiomazin (SALAR p)                            | Propiomazine                                                 |

*eTable 2a. Variable selection. Clinical variables

| Variable                                              | No of cases | Subject for PCA | Excl. after PCA | Subject for backward stepwise Cox-regression |
|-------------------------------------------------------|-------------|-----------------|-----------------|---------------------------------------------|
| Age, years (cont.)                                    | -           | Yes             | Yes             |                                             |
| Female, (man/woman)                                  | -           | Yes             | Yes             |                                             |
| Creatinine clearance, ml/min (cont.)                  | -           | Yes             | Yes             |                                             |
| Social support (living alone or with spouse /living in nursing home) | 301a       | Yes             | Yes             |                                             |
| Heart failure (yes/no)                               | 141         | Yes             | Yes             |                                             |
| Diabetes (yes/no)                                    | 88          | Yes             | Yes             |                                             |
| Pulmonary disease (yes/no)                           | 45          | Yes             | Yes             |                                             |
| Arrhythmia (yes/no)                                  | 142         | Yes             | Yes             |                                             |
| Malignant disease -past and present (yes/no)         | 61          | Yes             | Yes             |                                             |
| Coronary artery disease (yes/no)                     | 114         | Yes             | Yes             |                                             |
| Cerebral vascular lesion –past (yes/no)              | 72          | Yes             | Yes             |                                             |
| Myocardial infarct –past (yes/no)                    | 98          | Yes             | Yes             |                                             |
| Hypertension (yes/no)                                | 147         | Yes             | Yes             |                                             |
| Dementia (yes/no)                                    | 51          | Yes             | Yes             |                                             |

*(no of patients living alone or with spouse). PCA=principal component analysis)
**eTable 2b. Variable selection. Drug variables (the medications used by patients, categorized according to ATC classification system or SALAR drug classes; STOPP START criteria).**

| Variable (ATC code class/SALAR drug class/ STOPP and START criteria) | Drug                                                                 | No of cases | Subject for PCA | Excl. after PCA | Subject for backward stepwise Cox-regression |
|---|---|---|---|---|---|
| A02A | Antacid drugs | 4 | | | |
| A02B (A02BA + A02BC) | Drugs for peptic ulcer and gastro-esophageal reflux disease | 120 | Yes | Yes | |
| A03AX13 | Drugs for functional gastrointestinal disorders; Dimetikon | 4 | | | |
| A03FA01 | Propulsives; Metoclopramide | 13 | Yes | Yes | |
| A06AB | Laxatives (contact) | 32 | Yes | Yes | |
| A06AC+A06AD | Laxatives (bulk-forming and osmotically acting) | 129 | Yes | Yes | |
| A07DA03 | Antipropulsives; Loperamide | 8 | | | |
| A07EC | Intestinal antiinflammatory agents; aminosalicylic acid and similar | 4 | | | |
| A09A | Digestives | 2 | | | |
| A10A | Insulins and analogues | 54 | Yes | Yes | |
| A10BA02 | Oral blood glucose lowering drugs, excl. insulins; Metformin | 15 | Yes | Yes | |
| A10BB | Oral blood glucose lowering drugs, excl insulines; Sulfonureids | 39 | Yes | Yes | |
| A10BX | Oral blood glucose lowering drugs, excl. insulins; Other | 2 | | | |
| A11 | Vitamins | 27 | Yes | Yes | |
| A12A | Calcium supplement | 64 | Yes | Yes | |
| A12B | Potassium supplement | 19 | Yes | Yes | |
| A12C | Other mineral supplements | 11 | Yes | Yes | |
| B01AA03 | Antithrombotic agents – Warfarin | 44 | Yes | Yes | |
| B01AB | Antithrombotic agents – Heparin group | 7 | | | |
| B01AC | Antithrombotic agents – Platelet aggregation inhibitors excl heparin | 234 | Yes | Yes | |
| B03A | Iron preparations | 38 | Yes | Yes | |
| B03B | Vitamin B12 and folic acid | 190 | Yes | Yes | |
| B03X | Other anemiaic preparations | 13 | Yes | Yes | |
| C01A | Cardiac glycosides | 71 | Yes | Yes | |
| C01B | Antiarrhythmics | 4 | | | |
| C01CX | Cardiac stimulants excl. cardiac glycosides; Levosimendan | 1 | | | |
| C01DA | Vasodilators used in cardiac diseases; organic nitrates | 195 | Yes | Yes | |
| C02CA | Antihypertensives; alfa-adrenoreceptor blockers | 2 | | | |
| Variable (ATC code class/SALAR drug class/STOPP and START criteria) | Drug                                      | No of cases | Subject for PCA | Excl. after PCA | Subject for backward stepwise Cox-regression |
|-------------------------------------------------|-------------------------------------------|-------------|-----------------|-----------------|---------------------------------------------|
| C03                                             | Diuretics                                 | 318         | Yes             | Yes             |                                             |
| C05A                                            | Agents for treatment of hemorrhoids and anal fissures | 2           |                 |                 |                                             |
| C07A                                            | Beta blocking agents                      | 191         | Yes             |                 | Yes                                         |
| C08                                             | Calcium channel blockers                  | 69          | Yes             |                 | Yes                                         |
| C09                                             | Agents acting on the renin-angiotensin system | 189        | Yes             |                 | Yes                                         |
| C10                                             | Lipid modifying agents                    | 33          | Yes             |                 | Yes                                         |
| G03C                                            | Estrogens                                 | 27          | Yes             | Yes             |                                             |
| G04BD                                           | Other urologicals; drugs used in urinary incontinence | 5           |                 |                 |                                             |
| G04C                                            | Drugs used in benign prostate hyperplasi   | 17          | Yes             |                 | Yes                                         |
| H02A                                            | Corticosteroids for systemic use          | 36          | Yes             |                 | Yes                                         |
| H03                                             | Thyroid preparations                      | 45          | Yes             |                 | Yes                                         |
| J01                                             | Antibacterials for systemic use           | 7           |                 |                 |                                             |
| L01BA                                           | Cytostatic/cytotoxics; Folic acid analoges | 1           |                 |                 |                                             |
| L02B                                            | Endocrine therapy; Hormone antagonists and related agents | 5   |                  |                 |                                             |
| L04A                                            | Immunosuppressants                         | 1           |                 |                 |                                             |
| M01A                                            | Anti-inflammatory and antirheumatic products, non steriods | 19 | Yes | Yes | |
| M04A                                            | Anti-gout preparations                    | 30          | Yes             |                 | Yes                                         |
| M05BA                                           | Drugs affecting bone structure and mineralization; Bisfosfonates | 15 | Yes | Yes | |
| N02A                                            | Analgesics; Opioids                       | 68          | Yes             |                 | Yes                                         |
| N02B                                            | Analgesics; other analgetics              | 177         | Yes             |                 | Yes                                         |
| N02C                                            | Analgesics; antimigraine preparations      | 2           |                 |                 |                                             |
| N03A                                            | Antiepileptics                             | 5           |                 |                 |                                             |
| N04A+B                                           | Antiparkinson drugs                       | 19          | Yes             |                 | Yes                                         |
| N05A                                            | Antipsychotics                            | 34          | Yes             |                 | Yes                                         |
| N05BA                                           | Anxiolytics; Benzdiazapine derivates       | 64          | Yes             |                 | Yes                                         |
| N05BB01                                         | Anxiolytics; Hydroxizin                    | 5           |                 |                 |                                             |
| N05CD                                           | Hypnotics and sedatives; Benzdiazapine derivates | 12  |    | | |
| N05CF                                           | Hypnotics and sedatives; Benzdiazapine related agents | 113 | Yes | Yes | |
| N05CM                                           | Hypnotics and sedatives; Others            | 28          | Yes             |                 | Yes                                         |
| N06AC                                           | Antidepressants; Tricyclic antidepressants | 5           |                 |                 |                                             |
| N06AB+AX                                         | Antidepressants; SSRI+others              | 83          | Yes             |                 | Yes                                         |
| N06B                                            | Psychostimulants                          | 1           |                 |                 |                                             |
| N06D                                            | Anti-dementia drugs                       | 12          | Yes             |                 | Yes                                         |
| Variable (ATC code class/SALAR drug class/STOPP and START criteria) | Drug | No of cases | Subject for PCA | Excl. after PCA | Subject for backward stepwise Cox-regression |
|---------------------------------------------------------------|------|-------------|----------------|----------------|---------------------------------------------|
| R03AC | Drugs for obstructive airway diseases; Selective beta-2-stimulating agents | 46 | Yes | Yes | | |
| R03B | Drugs for obstructive airway diseases; Anticholinergic +corticosteroids | 51 | Yes | | Yes | |
| R03D | Drugs for obstructive airway diseases; Other (systemic) | 1 | | | | |
| R05 | Cough and cold preparations | 46 | Yes | | Yes | |
| R06A | Antihistamines for systemic use | 12 | Yes | | Yes | |
| S01B | Ophthalmicals | 39 | Yes | | Yes | |
| SALAR a | Anticholinergic agents | 34 | Yes | | Yes | |
| SALAR b | Long-acting benzodiazepine derivates | 12 | Yes | | Yes | |
| SALAR n | Neuroleptics | 26 | Yes | | Yes | |
| SALAR s | Oral NSAID | 14 | Yes | | Yes | |
| SALAR t | Tradolan | 27 | Yes | | Yes | |
| SALAR p | Propavan | 16 | Yes | | Yes | |
| STOPP a1 | | 29 | Yes | | Yes | |
| STOPP a2 | | 8 | | | |
| STOPP a4 | | 1 | | | |
| STOPP a6 | | 1 | | | |
| STOPP a7 | | 2 | | | |
| STOPP a8 | | 3 | | | |
| STOPP a11 | | 3 | | | |
| STOPP a12 | | 48 | Yes | | Yes | |
| STOPP a13 | | 7 | | | |
| STOPP b1 | | 2 | | | |
| STOPP b3 | | 2 | | | |
| STOPP b7 | | 11 | Yes | | Yes | |
| STOPP b8 | | 6 | | | |
| STOPP b9 | | 2 | | | |
| STOPP b12 | | 3 | | | |
| STOPP b13 | | 3 | | | |
| STOPP c1 | | 3 | | | |
| STOPP c4 | | 23 | Yes | | Yes | |
| STOPP e1 | | 2 | | | |
| STOPP e2 | | 3 | | | |
| STOPP e3 | | 2 | | | |
| STOPP e4 | | 5 | | | |
| STOPP e6 | | 2 | | | |
| STOPP e7 | | 8 | | | |
| STOPP f1 | | 2 | | | |
| STOPP f2 | | 1 | | | |
| STOPP f3 | | 1 | | | |
| STOPP g1 | | 8 | | | |
| STOPP g3 | | 3 | | | |
| STOPP g4 | | 12 | Yes | | Yes | |
| STOPP h1 | | 158 | Yes | | Yes | |
| STOPP h2 | | 28 | Yes | | Yes | |
| STOPP h3 | | 10 | Yes | | Yes | |
| STOPP h4 | | 13 | Yes | | Yes | |
| STOPP h5 | | 49 | Yes | | Yes | |
| Variable (ATC code class/SALAR drug class/STOPP and START criteria) | Drug | No of cases | Subject for PCA | Excl. after PCA | Subject for backward stepwise Cox-regression |
|---|---|---|---|---|---|
| STOPP i2 | 2 | 2 | Yes | Yes |
| STOPP j | 9 | 9 | | |
| START a1 | 7 | 7 | | |
| START a3 | 11 | Yes | Yes |
| START a5 | 1 | 1 | | |
| START a6 | 26 | Yes | Yes |
| START a7 | 9 | 9 | | |
| START a8 | 10 | Yes | Yes |
| START b1 | 5 | 5 | | |
| START c2 | 6 | 6 | | |
| START c3 | 12 | Yes | Yes |
| START f1 | 1 | 1 | | |
| START f2 | 5 | 5 | | |
| START f3 | 3 | 3 | | |

*Redundant with STOPP h5  **Redundant with R03B
PCA=principal component analysis
No patients scored positive on the STOPP criteria a3, a5, a9, a10, a14, a15, a16, 17, b2, b4, b5, b6, b10, b11, c2, c3, c5, d1, d2, d3, e5, e8, f3, f4, f6, g2, i1, i3 and START criteria a2, a4, b2, b3, c1, c2, c3, d1, d2, e1, f4.
**Supplementary Material:** Risk estimation from Cox model and from score sheet

**Formula**

\[
\text{Estimate of risk} = 1 - S_0(t) \exp \left( \sum \beta \chi - \sum \beta \chi_{\text{mean}} \right)
\]

- \( S_0(t) = 0.3215 \) (the average 1-year event-free time)
- \( \sum \beta \chi = \) the sum of the variables’ regression coefficients multiplied with actual value
- \( \sum \beta \chi_{\text{mean}} = \) the sum of the variables’ regression coefficients multiplied with mean/proportions

**Example**

A patient living in a nursing home with pulmonary disease and a kidney function of 55 ml/min, being prescribed a proton-pump-inhibitor.

1. Risk estimate based on the Cox model:

\[
\sum \beta \chi = -0.012 \times 55 + 0.481 \times 1 + 0.607 \times 1 + 0.506 \times 0 + 0.362 \times 1 + 0.724 \times 0 - 0.558 \times 0 = 0.79
\]

\[
\sum \beta \chi_{\text{mean}} = -0.012 \times 40.285 + 0.481 \times 0.182 + 0.607 \times 0.122 + 0.506 \times 0.166 + 0.362 \times 0.326 + 0.724 \times 0.179 - 0.558 \times 0.209 = -0.106842
\]

\[
\text{Estimate of risk} = 1 - 0.3215 \exp (0.79 + 0.106842) = 0.938
\]

2. Risk estimate based on the point score system:

- 1 point (nursing home) + 2 points (pulmonary disease) + 2 points (GFR 55 ml/min) + 1 points (drugs for peptic ulcer and GERD) = 6 points.

\[
\text{Estimate of risk} = 0.9568 \text{ (Table 4)}
\]

The points system gives a 1-year estimate of risk for rehospitalization or death of 96%, while using the Cox model directly gives an estimated risk of 94%. 
**eTable 3.** Statistical information of the 80+ score variables when tested for association with mortality

| Variable                                      | Regression coefficient (SE) | Mean or proportion | p-value | HR    | 95% CI for HR |
|-----------------------------------------------|----------------------------|--------------------|---------|-------|---------------|
| eGFR* (per mL/min/1.73m²)                     | -0.017 (0.006)             | 40.285             | 0.004   | 0.983 | 0.972-0.994   |
| Social support (living in nursing home vs living alone or with spouse) | 1.134 (0.205)             | 0.182              | 0.000   | 3.107 | 2.081-4.640   |
| Pulmonary disease* (vs. not)                  | 0.108 (0.283)             | 0.122              | 0.701   | 1.114 | 0.641-1.939   |
| Malignant disease* (vs. not)                  | 0.619 (0.223)             | 0.166              | 0.005   | 1.858 | 1.200-2.875   |
| Prescription of drug for peptic ulcer and GERD (vs. not) | 0.236 (0.194)             | 0.326              | 0.225   | 1.266 | 0.865-1.852   |
| Prescription of opioid drug (vs. not)         | 0.527 (0.216)             | 0.179              | 0.015   | 1.694 | 1.109-2.587   |
| Prescription of non-TCA-antidepressant drug (vs. not) | -0.209 (0.208)             | 0.209              | 0.315   | 0.812 | 0.540-1.219   |

*Cockcroft–Gault formula estimated glomerular filtration rate, *asthma or chronic obstructive pulmonary disease (COPD), *past or present

SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease, TCA=tricyclic antidepressants (TCA)