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BRIEF REPORT

Drug-related readmissions in older hospitalized adults: External validation and updating of OPERAM DRA prediction tool

Birgitta M. G. Snijders MD[1] | **Thomas G. H. Kempen PhD**[2,3] | **Carole E. Aubert MD, MSc**[4,5] | **Huiberdina L. Koek MD, PhD**[1] | **Olivia Dalleur PhD**[6,7] | **Jacques Donzé MD, MSc**[4,8,9,10] | **Nicolas Rodondi MD, MAS**[4,5] | **Denis O'Mahony MD, FRCPI, FRCP**[11,12] | **Ulrika Gillespie PhD**[2,13] | **Wilma Knol MD, PhD**[1]

[1]Department of Geriatrics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[2]Department of Pharmacy, Uppsala University, Uppsala, Sweden

[3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[4]Department of General Internal Medicine, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland

[5]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[6]Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium

[7]Pharmacy Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

[8]Department of Internal Medicine, Neuchatel Hospital Network, Neuchâtel, Switzerland

[9]Division of internal medicine, Lausanne University Hospital, CHUV, Lausanne, Switzerland

[10]Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[11]Department of Medicine (Geriatrics), University College Cork, Cork, Ireland

[12]Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland

[13]Hospital Pharmacy Department, Uppsala University, Uppsala, Sweden

Correspondence
Birgitta M. G. Snijders, Department of Geriatrics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
Email: b.m.g.snijders@umcutrecht.nl

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Abstract

Background: Drug-related readmissions (DRAs) are defined as rehospitalizations with an adverse drug event as their main or significant contributory cause. DRAs represent a major adverse health burden for older patients. A prediction model which identified older hospitalized patients at high risk of a DRA <1 year was previously developed using the OPERAM trial cohort, a European cluster randomized controlled trial including older hospitalized patients with multimorbidity and polypharmacy. This study has performed external validation and updated the prediction model consequently.

Methods: The MedBridge trial cohort (a multicenter cluster randomized crossover trial performed in Sweden) was used as a validation cohort. It consisted of 2516 hospitalized patients aged ≥65 years. Model performance was

assessed by: (1) discriminative power, assessed by the C-statistic with a 95% confidence interval (CI); (2) calibration, assessed by visual examination of the calibration plot and use of the Hosmer–Lemeshow goodness-of-fit test; and (3) overall accuracy, assessed by the scaled Brier score. Several updating methods were carried out to improve model performance.

Results: In total, 2516 older patients were included in the validation cohort, of whom 582 (23.1%) experienced a DRA <1 year. In the validation cohort, the original model showed a good overall accuracy (scaled Brier score 0.03), but discrimination was moderate (C-statistic 0.62 [95% CI 0.59–0.64]), and calibration showed underestimation of risks. In the final updated model, the predictor "cirrhosis with portal hypertension" was removed and "polypharmacy" was added. This improved the model's discriminative capability to a C-statistic of 0.64 (95% CI 0.59–0.70) and enhanced calibration plots. Overall accuracy remained good.

Conclusions: The updated OPERAM DRA prediction model may be a useful tool in clinical practice to estimate the risk of DRAs in older hospitalized patients subsequent to discharge. Our efforts lay the groundwork for the future development of models with even better performance.

KEYWORDS

drug-related readmission, external validation, older patient, prediction model

INTRODUCTION

Drug-related readmissions (DRAs) are a concern for older patients and a burden for society as they are associated with adverse clinical and economic outcomes.[1–3] In this study, DRAs are defined as rehospitalizations with an adverse drug event as their main or major contributory cause. They may include injuries resulting from medication use, including adverse drug reactions and medication errors. Up to two thirds of DRAs are considered preventable.[2]

Several medication optimization interventions have been developed with the aim of reducing DRAs in older hospitalized patients. These include the OPERAM (Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults) trial, the SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons) trial, and the MedBridge (Medication Reviews Bridging Healthcare) trial.[3–5] However, none of these interventions has significantly reduced the number of DRAs. There are many possible explanations for why these trials have not yet succeeded in reducing readmissions. For example, DRAs are a relatively subjective outcome for which no standardized measurements exist across studies. In addition, the reliability of the measurement methods used is unclear, and the study populations

Key points

- Identifying older patients at a high risk of drug-related readmissions (DRAs) may help to efficiently select patients most likely to benefit from medication optimization interventions during hospitalization.
- The (updated) OPERAM DRA prediction model can be used in clinical practice to aid healthcare professionals to estimate the risk of DRAs within 1 year in older hospitalized patients.
- Future research should focus on whether high-risk patients identified through this model actually benefit from medication optimization.

Why does this paper matter?

The updated OPERAM DRA prediction tool is a valuable tool that provides insights for healthcare professionals into the risk of DRAs. Identifying patients at a high risk of DRAs may assist in clinical decision making, for example prioritizing these patients for medication optimization interventions.

are highly heterogeneous.[3,4] Identifying patients at high risk of DRAs may help to select those patients most likely to benefit from medication optimization interventions during hospitalization and to design more focused interventions.

Recently, a prediction model which identifies older hospitalized patients at high risk of DRAs <1 year has been developed using the OPERAM cohort.[3,6] This prediction model has not yet been externally validated. To increase its value for clinical practice, the present study undertook external validation and updating of the OPERAM DRA prediction tool.

METHODS

Study design

The study design is an external validation study of an existing prediction model. Furthermore, the model was updated using the external validation cohort. Ethical approval for this study was waived by the Dutch Medical Research Ethics Committee NedMec (number 22/044).

Derivation and validation cohort

The DRA prediction model was previously developed using the OPERAM trial cohort.[3] The OPERAM study was a cluster randomized controlled trial (performed in Belgium, Ireland, the Netherlands, and Switzerland) that evaluated the effect of a structured pharmacotherapy optimization intervention on the incidence of DRAs <1 year. The study included 2008 hospitalized patients ≥70 years with multimorbidity and polypharmacy. External validation and updating was performed using the MedBridge trial cohort. The MedBridge study was a Swedish multicenter cluster randomized crossover trial that evaluated the effects of hospital-based comprehensive medication reviews with or without postdischarge follow-up.[4] The study population consisted of 2637 patients ≥65 years. Further details of both cohorts are provided in Supplement 1.

Prediction model

The OPERAM DRA prediction model was developed to predict DRAs in older patients <1 year after hospitalization.[6] Predictors used in the model include: the number of previous hospitalizations within the previous 12 months (categorized as 0, 1–2, ≥3); non-elective admission; history of hypertension; history of chronic kidney disease (CKD); history of cirrhosis with portal hypertension; the use of diuretics at admission; and the use of oral corticosteroids at admission. During development of the model, the authors assigned each predictor a value based on their regression coefficient. The total score ranged between −1 and 12 points and low- and high-risk categories were established based on the upper quartile (total score <3 and ≥3 points, respectively).

Statistical analysis

Participants from the interventions and control groups of the MedBridge study were included in the external validation cohort, since the intervention did not significantly affect the incidence of DRAs. During subanalyses, the predictive ability of the model was also evaluated separately in the control group and differences were explored. Further subanalysis was performed for patients ≥70 years. Study participants who died during index hospitalization were excluded from the analysis, since they could not be readmitted. A sensitivity analysis was performed with the aim of quantifying the potential bias of the competing risk of death (Supplement 2).

Predictive performance

The total score and predicted probabilities of a DRA <1 year were calculated for each patient. Model performance was assessed using the following measurements: (1) discriminative power, assessed by the C-statistic with a 95% confidence interval (CI); (2) calibration, assessed by visual examination of the calibration plot and the Hosmer–Lemeshow goodness-of-fit test (with a significant *p*-value indicating an overall lack-of-fit); and 3) overall accuracy, assessed by the scaled Brier score (the lower the score, the better, with a maximum score of 0.18 in this study).[7] The underlying regression equation was used to assess the C-statistic, the Hosmer–Lemeshow goodness-of-fit, and the scaled Brier score.

No patients had missing outcome data. When the proportion of missing predictor data was assessed, three patients (0.1%) were found to have missing predictor values. Therefore, model performance was evaluated using complete case analysis.

Updating methods

Several updating methods were used to further improve predictive performance. The MedBridge cohort was randomly split into an updating and testing set (80%/20%): the updating methods were applied to the updating set and its model performance was validated both internally

TABLE 1 Baseline characteristics according to drug-related hospital readmissions within 1 year in the OPERAM and MedBridge cohorts.

	OPERAM trial ($n = 1879$) Derivation cohort		MedBridge trial ($n = 2516$) External validation cohort	
Characteristic	**DRA ($n = 435$)**	**No DRA ($n = 1444$)**	**DRA ($n = 582$)**	**No DRA ($n = 1934$)**
Age in years	79.8 (±6.5)	79.3 (±6.2)	81.2 (±7.8)	80.2 (±8.1)
Female	179 (41.2%)	656 (45.4%)	300 (51.5%)	993 (51.3%)
Non-elective admission	360 (82.8%)	1078 (74.7%)	558 (95.9%)	1834 (94.8%)
Length of stay in days	11.5 (±10.4)	12.2 (±15.1)	12.8 (±14.0)	11.9 (±13.4)
≥1 hospitalization <1 year	267 (61.4%)	697 (48.3%)	305 (52.4%)	655 (33.9%)
Comorbidities				
Atrial fibrillation	108 (43.2%)	498 (34.5%)	234 (40.2%)	449 (23.2%)
Congestive heart failure	149 (34.3%)	362 (25.1%)	242 (41.6%)	424 (21.9%)
Chronic kidney disease	157 (36.1%)	390 (27.0%)	93 (16.0%)	195 (10.1%)
CVA or TIA	126 (29.0%)	415 (28.7%)	70 (12.0%)	202 (10.4%)
Diabetes	111 (25.5%)	309 (21.4%)	217 (37.3%)	501 (25.9%)
Chronic obstructive pulmonary disease	140 (32.2%)	364 (25.2%)	125 (21.5%)	221 (11.4%)
Hypertension	283 (65.1%)	1040 (72.0%)	440 (75.6%)	1307 (67.6%)
Cirrhosis with portal hypertension	9 (2.1%)	9 (0.6%)	1 (0.2%)	4 (0.2%)
Polypharmacy	435 (100%)	1444 (100%)	496 (85.2%)	1365 (70.6%)[a]
Medication				
Use of diuretics	247 (56.8%)	690 (47.8%)	285 (49.0%)	588 (30.4%)[a]
Use of oral corticosteroids	86 (19.8%)	168 (11.6%)	85 (14.6%)	180 (9.3%)[a]

Note: Categorical variables are presented as number (%) and continuous variables as mean with standard deviation.
Abbreviations: CVA, cerebrovascular accident; DRA, drug-related readmission; MedBridge, Medication Reviews Bridging Healthcare; OPERAM, Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Patients; TIA, transient ischemic attack.
[a]Three patients in this group had missing values (0.1%).

in the updating set and externally in the testing set. Updating methods ranged from parsimonious recalibration techniques to selective reduction and extension of predictors with re-estimation of the intercept and regression coefficients. The different updating methods are described in detail in Supplement 3. The final updated prediction model was chosen based on model performance characteristics. The optimal cut-off value, which identifies patients at high risk for DRAs in the final updated model, was determined by exploring the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio with their 95% CIs of different cut-off values.

All statistical analyses were performed using R statistical software (version 4.0.3).

RESULTS

The MedBridge cohort consisted of 2637 patients, of whom 121 (4.6%) died during index hospitalization and were excluded from further analysis. In total, 2516 patients were included from the external validation cohort. Baseline characteristics are presented and compared with those of the OPERAM cohort in Table 1. During one-year follow-up, 550 patients (21.9%) died, of whom 134 (24.4%) experienced a DRA before death. Within 1 year, 582 patients (23.1%) experienced a DRA. The total prediction score had a median of 1 (IQR 0–2) and ranged from −1 to 8 points.

Model performance

Model performance was evaluated using complete-case analysis including 2513 patients. Discrimination was moderate with a C-statistic of 0.62 (95% CI 0.59–0.64). Calibration plots showed systematic underestimation of risks (Figure 1 and Supplement 4). The Hosmer–Lemeshow test gave a p-value <0.001, indicating a lack-of-fit. The scaled Brier score was 0.03, suggesting good overall accuracy. Subgroup analyses performed for the control group and patients ≥70 years yielded similar results (Supplement 5).

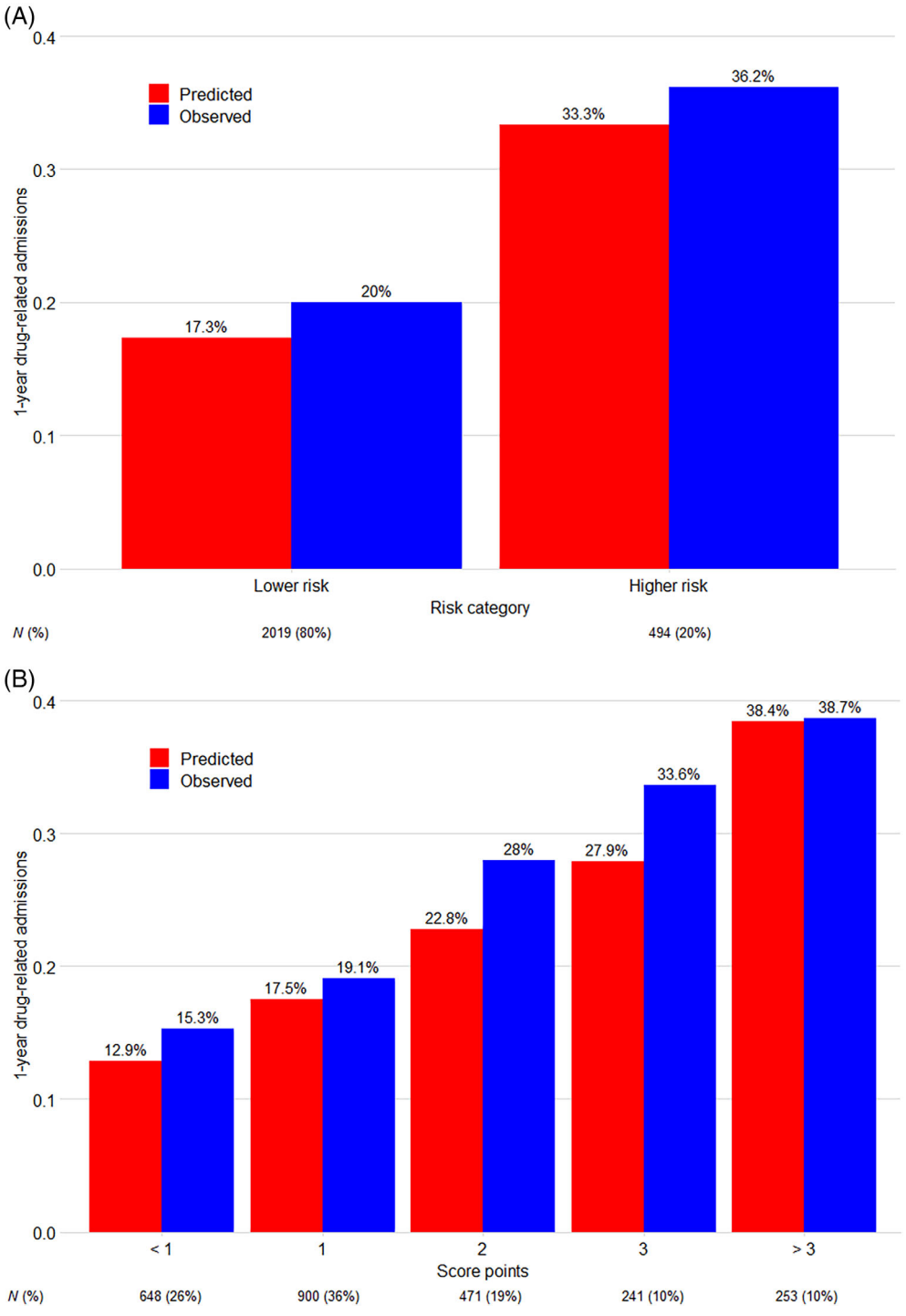

FIGURE 1 Calibration plots of the original prediction score based on risk category and scoring points to predict 1-year drug-related readmission in the external validation cohort. *N* = number of patients. (A) Calibration of the prediction model based on risk category. (B) Calibration of the prediction model based on scoring points.

Model updating

The distribution of baseline characteristics and predictor values, and the outcome of the updating and testing set of the MedBridge cohort, are shown in Supplement 6, Table S2. An overview of the adjusted intercepts and regression coefficients per updating method is shown in Supplement 6, Table S3. Table 2 summarizes the model performance for each updating method in both the updating and testing set and compares these findings with the performance of the original model. Calibration plots for each updating method are shown in Supplement 6, Figure S7. More extended updating methods yielded better model performance characteristics.

Polypharmacy is considered a relatively strong risk factor for DRAs in the literature and was therefore seen as an additional value to the existing model, thus Model

TABLE 2 Model performance of original prediction model in OPERAM cohort and each updating method in the updating and testing set of the MedBridge cohort.

	OPERAM cohort (n = 1879)	MedBridge cohort (n = 2513)							
		Method 0	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6[a]	Method 7
Updating set (n = 2010)									
C-statistic (95% CI)	0.64 (0.61–0.67)	0.62 (0.59–0.65)	0.62 (0.59–0.65)	0.62 (0.59–0.65)	0.66 (0.63–0.69)	0.62 (0.59–0.65)	0.66 (0.63–0.69)	**0.67 (0.64–0.70)**	0.67 (0.64–0.70)
HL p-value	0.82	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	**<0.001**	<0.001
Scaled Brier score	0.05	0.03	0.03	0.03	0.05	0.03	0.05	**0.06**	0.06
Testing set (n = 503)									
C-statistic (95% CI)	–	0.60 (0.55–0.66)	0.60 (0.55–0.66)	0.60 (0.54–0.66)	0.65 (0.59–0.70)	0.61 (0.55–0.66)	0.65 (0.59–0.70)	**0.64 (0.59–0.70)**	0.65 (0.60–0.71)
HL p-value	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	**<0.001**	<0.001
Scaled Brier score	–	0.03	0.03	0.01	0.05	0.02	0.05	**0.05**	0.06

Note: Method 6 was chosen for the final updated model.
Abbreviations: CI, confidence interval; HL, Hosmer–Lemeshow goodness-of-fit test.
[a]Method 6 was chosen for the final updated model (in bold).

6 was chosen as the final updated model.[8–11] Model 6 improved discriminative ability slightly (C-statistic 0.64 [95% CI 0.59–0.70]), and calibration plots considerably. The model performance characteristics for different cut-off values are shown in Supplement 6, Table S4. A high cut-off value, selecting the 10% of patients at highest risk, resulted in a high specificity (92.5%), but poor sensitivity (18.4%). The logistic regression equation of the final updated model and an example of its usage is shown in Supplement 6. Sensitivity analysis demonstrates that the competing risk of death does not negatively affect the association between predictors and the risk of DRAs of the updated model (Supplement 2).

DISCUSSION

This study evaluated the model performance of the OPERAM DRA prediction tool in an external validation cohort and has further updated the model to improve its performance. Model performance in the external validation cohort is comparable to that in the derivation cohort. In both cohorts, a good overall accuracy can be observed and the discriminative abilities are nearly equal. However, the calibration is worse as calibration plots show an underestimation of risks and a significant Hosmer–Lemeshow result indicating lack-of-fit. This finding is not unexpected since the model was developed using another cohort and is therefore less calibrated as a result. Several updating methods were performed, ranging from parsimonious methods to selective reduction and extension of predictors with re-estimation of the intercept and regression coefficients. The final model includes the following predictors: number of previous hospitalizations <1 year, non-elective admission, history of hypertension, history of CKD, use of diuretics at admission, use of oral corticosteroids at admission, and polypharmacy. This slightly improves the discriminative ability of the model. Calibration plots have improved considerably. Although the Hosmer–Lemeshow test remains statistically significant, calibration is best assessed graphically.[12] The overall accuracy is good.

The ideal cut-off point for the final updated model depends on the purpose of screening. If the aim is to minimize undertreatment, a high sensitivity would be preferred. However, both the OPERAM and MedBridge trials demonstrated that performing multicomponent medication interventions in all older hospitalized patients did not significantly affect the incidence of DRAs <1 year.[3,4] Performing these interventions is considered rather time-consuming; hence minimizing undertreatment may be neither preferable nor feasible

in clinical practice. A high specificity will result in few false positive tests and therefore minimize overtreatment, suggesting a cut-off of 10% to be optimal. We have reported the predictive abilities of the model for different cut-offs so users can determine their own ideal cut-off point depending on the purpose of screening.

There are some noteworthy differences between the original model and its updated version. It is not surprising that the updated model has been enhanced by the use of "polypharmacy" as a predictor, since this value was not evaluated during development of the original model and is a well-known risk factor for DRAs.[8–11] "Hypertension" was a protective factor in the original model, but is considered a risk factor, albeit a relatively small and non-significant one, in the updated model, which is in agreement with previous literature.[8] "A history of CKD" was a risk factor in the original model, but becomes a protective factor in the updated model, which is in contrast with previous literature.[9] The prevalence of CKD is higher in patients who developed a DRA <1 year (Table 1). As the regression coefficient of the predictor CKD is relatively small, its negative value is likely due to overcorrection.

To our knowledge, only one other prediction model has been developed and validated with the aim of identifying patients at high risk for DRAs. The Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (PADR-EC) score was developed for older hospitalized patients in Tasmania, Australia. It includes the following predictors: drug changes <3 months, renal failure, dementia, number of antihypertensives, and anticholinergics use.[13] Model performance was evaluated by assessing discrimination (C-statistic 0.67 [95% CI 0.56–0.78]).[13] Although its discrimination is slightly better in comparison to our model, its CI is relatively wide and other performance characteristics such as calibration were not assessed. Predictors like dementia or recent drug changes may not be readily available at the emergency department, thus making this score less feasible in clinical practice. This makes the (updated) OPERAM DRA prediction model a valuable addition.

This study is subject to some limitations. First, the model was validated and updated using both the control and interventions arms. As the interventions are intended to reduce DRAs, this may have affected the reliability of our findings. However, such interventions did not significantly affect the incidence of DRAs and a subgroup analysis performed in the control arm yielded similar results. During updating methods where re-estimation was performed, we adjusted for the randomization group. In addition, the model was developed in patients ≥70 years, but validated in patients ≥65 years. Nevertheless, we included the whole cohort, with the aim of increasing the model's generalizability, since a subanalysis in patients ≥70 years showed similar results. As both trials used different methods to identify DRAs, this may have affected our results. A DRA is a relatively subjective outcome compared with "hard" outcomes such as mortality, and its measurement is therefore limited by subjective considerations. However, the incidence of DRAs was 23% in both trials, which is in accordance with a recent systematic review that reports a prevalence of 21%.[2] This may imply that, although the trials used different methods, they identified DRAs in a similar way. Another limitation is that the presence of predictor values in both cohorts was determined based on diagnoses and medications registered in the patients' electronic health records. These data were not checked with patients or their healthcare providers, which raises the question of whether the prevalences reported adequately reflect clinical practice.

A strength of this study is that the model was developed, validated, and updated using two large prospective cohorts with few exclusion criteria, including patients from five different European countries, which increases its generalizability to other populations. The model has also been validated in the general older hospitalized population. The predictor values are easily obtainable, making the model feasible in clinical practice. In addition, the cohorts have few missing values, minimizing the risk of bias.

Development of a robust prediction model is challenging, especially in older populations. The occurrence of DRAs is often the result of a multifactorial process in which a combination of risk factors leads to hospitalization. Due to the heterogeneity of groups of older adults, there are many potential risk factors for DRAs that may be mutually related to one another.[8] This makes predictive risk modeling more difficult than for younger populations.

The updated OPERAM DRA prediction model can be used to assist in identifying older hospitalized patients at risk for DRAs <1 year with good accuracy and acceptable discrimination. This is the first model aimed at identifying patients at a high risk of DRAs that has been externally validated and updated. Our efforts lay the groundwork for the future development of models with even better performance. This prediction model can be used in clinical practice to provide insights for healthcare professionals into the risk of DRAs and increase awareness for medication-related adverse events. However, the results should be interpreted with caution, as the discriminative ability of

the model is moderate. Future research should explore potential risk factors that have not been included in this research, such as drug–drug interactions, to evaluate whether these factors may further enhance predictive performance.[8] Another important step is to evaluate whether high-risk patients identified through this method actually benefit from medication optimization.

AUTHOR CONTRIBUTIONS

All authors who have contributed significantly to this work have been included in this section and have given their written consent for submission. *Conception and design of study*: Birgitta M. G. Snijders, Thomas G. H. Kempen, Carole E. Aubert, Huiberdina L. Koek, Olivia Dalleur, Jacques Donzé, Nicolas Rodondi, Denis O'Mahony, P.M.J. Welsing (methodologist UMC Utrech), Ulrika Gillespie, Wilma Knol. *Preparation of MedBridge database*: A.N. Hedman (research assistant at Pharmacy Department, Uppsala University Hospital), Thomas G. H. Kempen. *Data analysis and interpretation of data*: Birgitta M. G. Snijders, Huiberdina L. Koek, Wilma Knol. *Manuscript drafting*: Birgitta M. G. Snijders, Huiberdina L. Koek, Wilma Knol. *Revising the manuscript critically for important intellectual content*: Birgitta M. G. Snijders, Thomas G. H. Kempen, Carole E. Aubert, Huiberdina L. Koek, Olivia Dalleur, Jacques Donzé, Nicolas Rodondi, Denis O'Mahony, Ulrika Gillespie, Wilma Knol.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Not applicable.

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ORCID

Birgitta M. G. Snijders https://orcid.org/0000-0002-3605-2289
Carole E. Aubert https://orcid.org/0000-0001-8325-8784

REFERENCES

1. Lim R, Ellett LMK, Semple S, Roughead EE. The extent of medication-related hospital admissions in Australia: a review from 1988 to 2021. *Drug Saf*. 2022;45(3):249-257.
2. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and preventability of drug-related hospital readmissions: a systematic review. *J Am Geriatr Soc*. 2018;66(3):602-608.
3. Blum MR, Sallevelt B, Spinewine A, et al. Optimizing therapy to prevent avoidable hospital admissions in multimorbid older adults (OPERAM): cluster randomised controlled trial. *BMJ*. 2021;374:n1585.
4. Kempen TGH, Bertilsson M, Hadziosmanovic N, et al. Effects of hospital-based comprehensive medication reviews including postdischarge follow-up on older patients' use of health care: a cluster randomized clinical trial. *JAMA Netw Open*. 2021;4(4):e216303.
5. O'Mahony D, Gudmundsson A, Soiza RL, et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. *Age Ageing*. 2020;49(4):605-614.
6. Aubert CE, Rodondi N, Netzer S, et al. Predictors of 1-year drug-related admissions in older multimorbid hospitalized adults. *J Am Geriatr Soc*. 2022;70(5):1510-1516.
7. Steyerberg E. *Clinical Prediction Models*. Vol XXXIII. 2nd ed. Springer Cham; 2019:558.
8. Ayalew MB, Tegegn HG, Abdela OA. Drug related hospital admissions; a systematic review of the recent literatures. *Bull Emerg Trauma*. 2019;7(4):339-346.
9. Leendertse AJ, Egberts AC, Stoker LJ, Van Den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med*. 2008;168(17):1890-1896.
10. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother*. 2008;42(7):1017-1025.
11. Kempen TGH, Hedman AN, Hadziosmanovic N, et al. Risk factors for and preventability of drug-related hospital revisits in older patients: a post-hoc analysis of a randomized clinical trial. *Br J Clin Pharmacol*. 2022;89(5):1575-1587.
12. Moons KG, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.
13. Parameswaran Nair N, Chalmers L, Connolly M, et al. Prediction of hospitalization due to adverse drug reactions in elderly community-dwelling patients (the PADR-EC score). *PLoS One*. 2016;11(10):e0165757.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplement 1. Details on OPERAM and MedBridge cohort.

Supplement 2. Sensitivity analysis.
Supplement 3. Methods for prediction model updating.
Supplement 4. Calibration plot original prediction model.
Supplement 5. Subgroup analyses.
Supplement 6. Methods for prediction model updating.

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