Research in Social and Administrative Pharmacy 20 (2024) 926–933

Contents lists available at ScienceDirect

Research in Social and Administrative Pharmacy

journal homepage: www.elsevier.com/locate/rsap

Original Research

Development and external validation of a prognostic model for time to readmission or death in multimorbid patients

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ARTICLE INFO

Keywords:
Integrated medicines management
Multimorbidity
Readmission
Prognostic model
Validation

ABSTRACT

Objective: To develop and externally validate a prognostic model built on important factors predisposing multimorbid patients to all-cause readmission and/or death. In addition to identify patients who may benefit most from a comprehensive clinical pharmacist intervention.

Methods: A multivariable prognostic model was developed based on data from a randomised controlled trial investigating the effect of pharmacist-led medicines management on readmission rate in multimorbid, hospitalised patients. The derivation set comprised 386 patients randomised in a 1:1 manner to the intervention group, i.e. with a pharmacist included in their multidisciplinary treatment team, or the control group receiving standard care at the ward. External validation of the model was performed using data from an independent cohort, in which 100 patients were randomised to the same intervention, or standard care. The setting was an internal medicines ward at a university hospital in Norway.

Results: The number of patients who were readmitted or had died within 18 months after discharge was 297 (76.9 %) in the derivation set, i.e. the randomized controlled trial, and 69 (71.1 %) in the validation set, i.e. the independent cohort. Charlson comorbidity index (CCI; low, moderate or high), previous hospital admissions within the previous six months and heart failure were the strongest prognostic factors and were included in the final model. The efficacy of the pharmaceutical intervention did not prove significant in the model. A prognostic index (PI) was constructed to estimate the hazard of readmission or death (low, intermediate or high-risk groups). Overall, the external validation replicated the result. We were unable to identify a subgroup of the multimorbid patients with better efficacy of the intervention.

Conclusions: A prognostic model including CCI, previous admissions and heart failure can be used to obtain valid estimates of risk of readmission and death in patients with multimorbidity.

1. Introduction

It is well known that in the multimorbid population with complex drug regimens, negative outcomes like unplanned hospital readmissions or mortality are difficult to avoid.[1–4] However, tailored health care services for this steadily increasing patient group has a great potential to improve patient health and reduce social costs e.g. by avoiding preventable outcomes.[5] Prognostic models to identify important factors predisposing to readmissions and deaths or prediction models to identify patients at risk would enable prioritizing time and resources to the patients who likely benefit the most of targeted interventions in the health care.

Integrated medicines management (IMM) is a comprehensive tailoring of drug therapy throughout the patient's hospital journey.[6] Currently, the procedure for selection of which patients should be prioritized for clinical pharmacy services is most often empirical.[7] The

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https://doi.org/10.1016/j.sapharm.2024.06.007
Received 5 November 2023; Received in revised form 23 May 2024; Accepted 19 June 2024
Available online 21 June 2024

often limited and expensive hospital clinical pharmacists' resources should be allocated to the patients who will benefit most.[7–9]

Prognostic models have been used to prognosticate medication related outcomes of individual patients or patient groups.[7,9] Classification of patients into risk groups may furthermore be applied to predict whether specific patients will have more benefit from an intervention, i.e. building ***predictive*** models. Prognostic factors are often patient characteristics, diseases, medications, and laboratory results.[7–11] However, recent systematic reviews highlight limitations in both the development and the validation processes of the existing prognostic models, as well as insufficient evidence of clinical usefulness.[7–11]

In Northern Ireland and Sweden, prognostic models have been developed in frail, elderly people, but not in multimorbid patients. These models are based on data from a cohort and a randomized controlled trial investigating comprehensive clinical pharmacist interventions.[12,13] In the internally validated Northern Irish model, comprising hospitalised patients with a median age of 70 years, prognostic factors of readmission or death 12 months post-discharge constituted the following variables: Age-adjusted co-morbidity score, receiving diuretics, number of admission medications, and previous admissions.[12]

In the Swedish "80 (years)+"-score, prognostic factors for revisits to hospital and mortality were impaired renal function, pulmonary or malignant disease, living in a nursing home, being prescribed an opioid or a drug for peptic ulcer or gastroesophageal reflux disease, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked to a lower risk.[13] However, it is unclear whether these factors are relevant for prognosis in multimorbid patients. Furthermore, in both prognostic models external validation is lacking, i.e. testing the models in independent study populations to ensure consistency of model performance and robustness before recommendation to clinical use. Ultimately, the *predictive* effect, i.e. identification of a group of patients that would benefit more from a comprehensive clinical pharmacist intervention has to our knowledge not been investigated.

The primary objective was to develop and externally validate a prognostic model built on important factors predisposing multimorbid patients to all-cause readmission and death. The secondary outcome was to identify patients who may benefit most from in-hospital tailored clinical pharmaceutical intervention.

2. Methods

2.1. Study participants and data

Patient data from a prospective randomised controlled trial (RCT) finalised in March 2016 were used to build the model, ClinicalTrials.gov Identifier: NCT02336113.[14,15] The main objective of the RCT was to investigate the effect of pharmacist-led medicines management in multimorbid, hospitalised patients on long-term hospital readmissions and survival.[15] Multimorbidity is broadly defined as the coexistence of two or more long-term health conditions.[2,3] The primary analysis population comprised 386 multimorbid patients which is also the derivation set for building the model. The patients had a median age of 79 years (range 23–96), were using minimum four regular drugs from minimum two therapeutic classes, and were acutely admitted to the internal medicine ward at Oslo University Hospital. The patients were randomised 1:1 to the intervention group, i.e. with a pharmacist included in their multidisciplinary treatment team, or the control group receiving standard care at the ward. Intervention patients received pharmacist-led medicines management comprising medicines reconciliation at admission, repeated medicine reviews throughout the stay and medicines reconciliation and tailored information at discharge according to the integrated medicines management model.[6,15]

To externally validate the model performance, inclusion of a new cohort of 100 patients from the same internal medicine ward was conducted January to July 2018, and this constituted the validation set. This sub-study had identical inclusion and exclusion criteria as the RCT, and randomisation between the same pharmacist intervention and standard care. All study pharmacists delivering the intervention in both the original RCT and the validation cohort, were experienced clinical pharmacists with training in IMM. In the original RCT a total of six study pharmacists contributed, and in the validation sub-study five study pharmacists contributed, whereof three also contributed to the original RCT.

All patients, i.e. both from the original RCT and the validation cohort, were followed for a minimum of 18 months after hospital discharge. Data on readmissions and deaths was collected from the Norwegian Patient Registry and the Norwegian Cause of Death Registry.

2.2. Ethics

This sub-study was approved as a protocol amendment to the original RCT's study protocol.[15] Ethical approval was obtained from the Regional Committee for Medical and Health Research Ethics (2014/704/REK south-eastern D) and the Privacy Ombudsman at Oslo University Hospital. Prior to inclusion, each patient gave written informed consent.

2.3. Outcome variables

The primary outcome measure was the same as in the original RCT, a composite variable, combining time to the *first* event, from the day of discharge from index admission, to either unplanned readmission or death during follow-up.[15]

2.4. Statistical analyses

2.4.1. Identification of prognostic and predictive factors

The modelling strategy was initiated by a visual inspection of all demographic, clinical, and medication specific variables that could be associated with time to readmission or death, i.e. Kaplan Meier plots. The selected candidate variables were chosen based on available literature on risk prediction and on clinical reasoning.[12–14,16] Data for all variables were collected at admission except Charlson comorbidity index score,[17] diagnoses and number of gene-drug interactions at admission, which were assessed retrospectively, based on data from the medical record, patients' genotype results and the reconciled drug list. Dichotomous variables with less than 10 patients in the smallest group were excluded. To build a robust model and avoid unstable parameter estimates, a maximum of 4–5 explanatory variables were to be included in the final model. Continuous independent variables were organised into categories to check for linearity and included in the final model based on best model fit. No imputation of missing values was performed.

2.4.2. Development of model/risk score

A risk score was developed in the derivation set by the following approach. All candidate variables with prognostic value were included in a Cox' proportional hazards model, by a combination of forward selection and backward elimination of variables. Covariates resulting in a p-value less than 0.2 in unadjusted analyses were candidates for the first step.[18] Treatment interactions were also assessed. The final model was restricted to include clinical variables thought to be biologically plausible as well as statistically significant at the 5 % level. The prognostic index (PI) was estimated based on the estimated coefficients from the model, and further categorized by three risk groups (low, intermediate, and high risk). The choice of decision thresholds, which are the cut-offs for risk prognosis (low, intermediate and high risk-groups), was guided by an intention to ease the use of the PI in clinical practice as well as keeping groups at about the same size. Hazard ratios (HRs) were presented with 95 % confidence intervals (CIs).

2.4.3. Identification of patients with larger effect of the IMM-intervention

To assess whether a group of patients could have a better effect of the

IMM intervention, we assessed the interaction between risk group and the intervention during the development stage in the derivation set. We also assessed any interaction between the intervention and each variable in the final model.

2.4.4. External validation of the model

The PI for each patient in the validation set was calculated using the parameters estimated in the derivation set. Patients were further categorized into three risk groups using the same cut-offs as in the derivation set. Kaplan-Meier (KM)-estimates and HRs for the three groups in the derivation set versus the validation set were compared, and discrimination measures (Harrell's c-index and Somer's D) were estimated.[19] The interaction between risk group and the intervention was also assessed.

Results are reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) reporting guidelines for prognostic model studies[20]

Statistical analyses were performed by IBM SPSS Software version 25.0 (IBM Corp. NY) and StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

3. Results

3.1. Overview of included patients

The initial RCT (derivation set) study population comprised 386 patients, aged 23 years or above who were admitted to the internal medicines ward during the study period, August 30, 2014 to March 17, 2016. The consort flow chart can be found in a previous publication.[15] The validation cohort was recruited on the same basis and comprised 97 discharged patients, admitted to the same ward in the period January 2, 2018 to June 28, 2018. **Supplement 1** shows the patient flow in the validation set. Table 1 presents baseline characteristics for all patients in the derivation and validation sets. The number of patients who were readmitted or had died within 18 months was 297 (76.9 %) in the randomized controlled trial (derivation set) and 69 (71.1 %) in the independent cohort (validation set).

3.2. Identification of prognostic and predictive factors

In total, 32 variables were subject to visual inspection by time to event analysis. The variables were demographic (n = 3), clinical (n = 8) and medication specific (n = 21), and unadjusted estimates of the association between each variable and time to outcome are shown in

Table 1
Patient characteristics.

Characteristic	Derivation set (386 patients)		Validation set (97 patients)	
	Control (193 patients)	Intervention (193 patients)	Control (49 patients)	Intervention (48 patients)
Women	106 (55 %)	102 (53 %)	27 (57 %)	30 (63 %)
Age	80.7 (23.1–96.4)	78.0 (25.7–95.6)	78.8 (31.5–93.9)	82.7 (19.8–96.3)
No of unplanned hospitalisations last 6 months	1 (0–6)	0 (0–11)	0 (0–4)	0 (0–3)
Charlson Comorbidity Index score	3 (0–12)	2 (0–11)	2 (0–8)	2 (0–7)
Most frequent medical history:				
- Hypertension	91 (47 %)	108 (56 %)	NA	NA
- Endocrine and metabolic diseases	77 (40 %)	80 (42 %)	NA	NA
- Kidney disease	63 (33 %)	73 (38 %)	NA	NA
- Congestive heart failure	81 (42 %)	68 (35 %)	18 (48 %)	20 (53 %)
- Arrhythmia	72 (37 %)	71 (37 %)	NA	NA
Body mass index[a]	24.4 (14.4–48.4)	25.0 (13.1–43.3)	28.4 (15.9–42.9)	24.1 (10.9–39.6)
Laboratory results:				
- Glomerular filtration rate (mL/min)[b]	49 (8–235)	52 (9–229)	62 (25–137)	54 (16–142)
- Serum albumin (g/L)[c]	38 (24–51)	38 (22–56)	40 (26–47)	39 (26–47)
- C reactive protein (nmol/L)	133 (0–3419)	152 (0–5248)	24 (0–338)	15 (0–290)
No of prescribed medications[d] at hospital admission:				
- Regular	8 (4–19)	8 (4–19)	8 (4–14)	8 (3–15)
- On demand	2 (0–10)	2 (0–11)	2 (0–9)	2 (0–8)
Assistance with medication administration before hospitalisation:				
- Multidose	51 (26 %)	46 (24 %)	10 (20 %)	19 (40 %)
- Home nurse	33 (17 %)	28 (15 %)	5 (10 %)	7 (15 %)
- Nursing home	15 (8 %)	15 (8 %)	0 (0 %)	6 (13 %)
- Relative	13 (7 %)	14 (7 %)	4 (8 %)	3 (6 %)
Home-dwelling before hospitalisation	178 (92 %)	178 (92 %)	46 (94 %)	34 (71 %)
No of medication-related problems	13 (3–31)	13 (3–42)	NA	NA
Length of index hospital stay, no of days	8 (2–57)	7 (1–66)	8 (3–57)	8 (2–30)
Total no of prescribed medications at hospital discharge	11 (3–24)	11 (3–23)	7 (0–12)	6 (0–13)
Discharged to home	124 (64 %)	129 (67 %)	36 (74 %)	30 (63 %)
Assistance with medication administration after discharge:				
- Multidose	28 (15 %)	26 (14 %)	3 (6 %)	5 (10 %)
- Home nurse	32 (17 %)	21 (11 %)	6 (12 %)	8 (17 %)
- Nursing home	51 (26 %)	51 (26 %)	11 (22 %)	17 (35 %)
- Relative	7 (4 %)	11 (6 %)	2 (4 %)	2 (4 %)
- Other institution/hospital ward	18 (9 %)	13 (7 %)	0 (0 %)	0 (0 %)

Data are n (%) or median (range).
NA: Information not available. The accuracy of diagnoses in the discharge summary were not quality assured in the validation set, as they had been in the derivation set and therefore were considered not comparable.

[a] Body mass index was registered for 144/193 control patients and 148/193 intervention patients in the derivation set, and for 39/49 control patients and 36/48 intervention patients in the validation set.

[b] calculated using the Cockcroft-Gault formula, except for obese patients (body-mass index >30), for whom the Salazar-Corcoran formula was used.

[c] Serum albumin was registered for 181/193 control patients and 187/193 intervention patients in the derivation set and for 48/49 control patients and 45/48 intervention patients in the validation set.

[d] After medicines reconciliation.

Table 2
Unadjusted association between potential prognostic factors[a] and time to readmission or death. HR = hazard ratio, CI = Confidence interval.

Variable	(Definition/units)	HR	95 % CI for HR
Demographic			
Sex	(male)	0.92	0.74 to 1.14
	(female)		
Age	<80 years	1.24	1.00 to 1.54
	≥80 years		
Previous admissions six months before index stay	(no/yes)	1.56	1.26 to 1.95
Clinical			
Charlson Comorbidity Index score	(1–2)		
	(3)	2.13	1.58–2.85
	(4 - ≥5)	2.76	2.15–3.56
Assistance with medication management before admission	(no/yes)	1.17	0.93 to 1.48
Body mass index	<25 kg/m^2	0.77	0.60 to 0.99
	≥25 kg/m^2		
Cancer	(no/yes)	1.95	1.50 to 2.53
Chronic obstructive pulmonary disease	(no/yes)	1.43	1.11 to 1.84
Heart failure	(no/yes)	1.82	1.46 to 2.29
Diabetes	(no/yes)	0.95	0.74 to 1.22
Medication specific			
No of prescribed drugs‡ at hospital admission:	(4–8)		
- Regular	(9-19)	1.57	1.26 to 1.95
- On demand	(0-11)	1.30	1.05 to 1.62
Gene-drug interactions	0	1.00	0.87 to 1.13
	1		
	>1		
Drugs for peptic ulcer and gastro-oesophageal reflux disease	(no/yes)	1.18	0.95 to 1.47
Medications for obstipation	(no/yes)	1.50	1.19 to 1.88
Antipropulsives	(no/yes)	1.35	0.80 to 2.26
Insulins and analogues for injection	(no/yes)	1.17	0.86 to 1.64
Blood glucose lowering drugs, excluding insulins	(no/yes)	0.90	0.66 to 1.22
Antithrombotic agents	(no/yes)	1.23	0.96 to 1.58
Digoxin	(no/yes)	1.47	0.90 to 2.35
Diuretics	(no/yes)	1.63	1.31 to 2.03
β-blockers	(no/yes)	1.19	0.96 to 1.49
Calcium channel blockers	(no/yes)	0.80	0.62 to 1.03
Angiotensin-converting enzyme inhibitors	(no/yes)	1.01	0.81 to 1.25
Lipid modifying agents	(no/yes)	0.78	0.63 to 0.97
Corticosteroids for systemic use	(no/yes)	1.36	1.05 to 1.77
Antiinfectives for systemic use	(no/yes)	0.92	0.66 to 1.27
Anti-inflammatory and antirheumatic products, non-steroids	(no/yes)	0.77	0.54 to 1.09
Opioids	(no/yes)	1.26	1.01 to 1.58
Antidepressants	(no/yes)	0.88	0.67 to 1.17
Medications for obstructive airway disease	(no/yes)	1.16	0.92 to 1.47

[a] The following variables were excluded: BMI (due to missing values on height and/or weight for 94 patients (24 %) in the derivation set and 22 patients (23 %) in the validation set), gene-drug interactions at admission (intersecting graphs), whether the patient was responsible for medication management prior to admission (intersecting graphs), drugs belonging to ATC group C09, N06A, A10A, A10B and B01A, J, R03 and H02 (intersecting graphs), or to ATC group C03, C07A and C01A_A05 (collinear with heart failure) and A06 (collinear with opioids).

Table 2. After visual inspection of the Kaplan Meier plots, 15 variables were excluded. Body Mass Index (BMI) was excluded because values on height and/or weight were missing in the medical record for 94 patients (24 %) in the derivation set and 22 patients (23 %) in the validation set. The exploratory data analysis resulted in a total of 18 variables being taken forward to the multivariate analysis stage. Descriptive information about the candidate prognostic factors is presented in **supplement 2**.

3.3. Development of PI

Eighteen variables were entered into the backward stepwise Cox regression, where only statistically significant variables (i.e. $\rho \leq 0.05$) were retained. This procedure identified five variables with prognostic value: Charlson comorbidity index, previous admissions six months before index stay (versus not), number of regular medications at hospital admission (dichotomous variable with 4–8 medications in one group and 9–19 medications in the other group), ATC group C10 lipid modifying agents (vs. not) and heart failure (vs. not). Due to lack of linear relationship, the Charlson comorbidity index was categorized into three levels of comorbidity, i.e. low = 1–2, moderate = 3, and high ≥4. For the other variables, the categories were assigned the value of 0 or 1, as in no or yes. In the subsequent selection of variables, the medication related variables (number of regular medications at hospital admission and lipid modifying agents) were excluded, acknowledging the practical challenges of having to perform medication reconciliation on all patients before the prognostic model can be used. Heart failure and previous

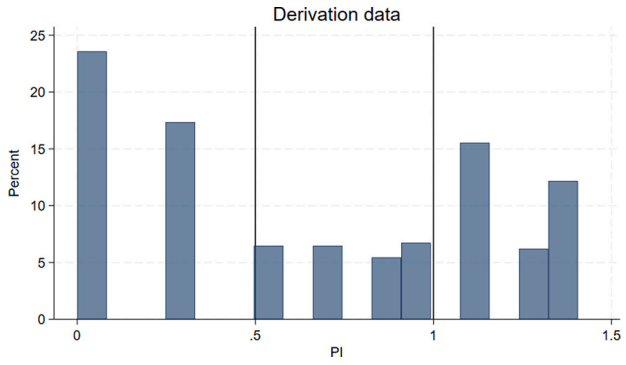

Fig. 1a. Distribution of the prognostic index (PI) in the derivation dataset. The vertical lines show decision thresholds, which are the cut-offs for risk prognosis (low, intermediate, and high risk).

Table 3
The full prognostic model. HR = hazard ratio, CI = Confidence interval.

Variable	β coefficient	HR	95 % CI (HR)	p value
Previous admissions	0.27	1.30	1.04–1.63	0.021
Congestive heart failure	0.29	1.34	1.06–1.70	0.015
Charlson comorbidity index score:				
1–2	0	1		
3	0.69	1.99	1.48–2.68	<0.001
≥4	0.85	2.33	1.78–3.05	<0.001

admissions were both associated with an increased hazard of readmission or death, as was Charlson comorbidity index score. The regression coefficients for these three clinical variables were subsequently used to calculate the final PI, presented below. Distribution of risk scores as well as cut-offs defining low, intermediate, or high risk are presented in Fig. 1a. Table 3 presents the full specification of the PI including coefficients.

$$PI = (0.29 \text{ x } chf) + (0.27 \text{ x } prev\ adm) + (0.69\ x\ C2) + (0.85\ x\ C3)$$

chf: congestive heart failure, yes = 1/no = 0

prev adm: previous admission 6 months before index admission, yes = 1/no = 0.

C2: = 1 if charlson comorbidity index score = 3, otherwise 0.

C3: = 1 if charlson comorbidity index score ≥4, otherwise 0.

3.4. Exploring whether the effect of the intervention can be predicted by prognostic group

After establishing the variables to be included in the model, we checked for treatment interactions. No interaction between prognostic group and the intervention was found. **Supplement 3** shows the Kaplan Meier plots for the three PI groups in the control and intervention group respectively, in the derivation and validation sets.

In the derivation set there were, however, signs that patients who had not been hospitalised before might benefit more from the intervention (HR 0.70, 95 % CI 0.51–0.96) than patients with frequent hospital admissions (HR 1.02, 95 % CI 0.76–1.37). An interaction term between the variable 'previous admissions six months before index stay' and 'the intervention' was therefore added in the model. However, we did not find any formally statistically significant interaction at the 5 % level (p = 0.089). Moreover, this finding was not confirmed in the validation set and this subgroup finding was not further pursued.

3.5. External validation and model performance

The distribution of the PI for the individual patients in the validation dataset, Fig. 1b, is very similar to the distribution of scores in the derivation data set. A visual comparison between Kaplan Meier plots for the

Fig. 1b. Distribution of the prognostic index (PI) in the validation dataset. The vertical lines show decision thresholds, which are the cut-offs for risk prognosis (low, intermediate, and high risk).

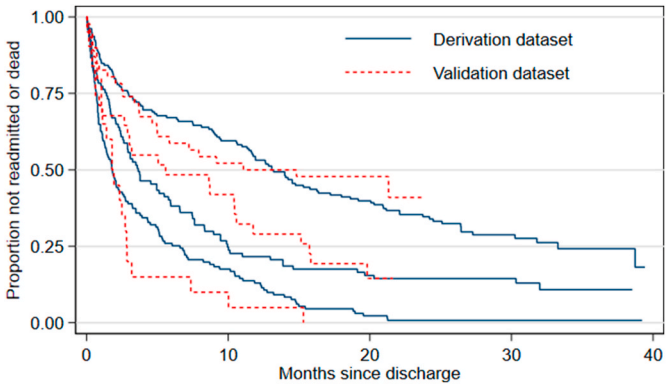

Fig. 2. Time to first hospital readmission or death in the three risk groups in the derivation and validation datasets, based on the prognostic model.

Table 4
Hazard ratios and discrimination measures in the derivation and validation datasets. All values are based on the prognostic index (PI) of the prognostic model. HR = hazard ratio, CI = Confidence interval.

Measure	Derivation dataset			Validation dataset		
	n	HR (95 % CI)	p-value	n	HR (95 % CI)	p-value
Low risk	158	1 (ref)		46	1 (ref)	
Intermediate risk	97	1.95 (1.47–2.59)	<0.001	31	1.97 (1.13–3.40)	0.016
High risk	131	3.26 (2.50–4.24)	<0.001	20	4.28 (2.29–8.00)	<0.001
Harrell c-index		0.631			0.622	
Somer's D		0.262			0.243	

derivation and validation data sets, Fig. 2, shows that the curves are quite well separated also in the validation data set. The model can thus identify high, intermediate, and low risk patients. Hazard ratios (with CIs) and the discrimination measures (Harrell's c-index and Somer's D) are given for both datasets in Table 4. The values are similar with well-maintained hazard ratios, and the discrimination is modest, supporting the visual impression.

4. Discussion

In the present study, we examined relationships between time to the first event of readmission or death and risk factors in vulnerable, multimorbid patients admitted to an internal medicine ward, to identify patients at risk of such events. Factors identified as prognostic were included in a regression model, and a PI was calculated. Patients were then classified as high, intermediate, or low risk according to their PI. We also aimed to see if we could select a subgroup of patients who had a particularly good effect of the comprehensive clinical pharmacist intervention.

4.1. Key findings

We have developed a prognostic model that we have succeeded to validate with external data. Distinct groups of multimorbid patients at risk of readmissions or death were identified: Patients with a moderate or high Charlson comorbidity index and/or previous admission(s) six months before index stay, and/or heart failure. The result was overall replicated in the external validation data. However, as no interaction between risk category and intervention was found we did not succeed in identifying patients who would benefit more from the comprehensive clinical pharmacist intervention.

4.2. Comparison with previous work

Most studies aiming to develop tools to identify patients whom should be prioritized by clinical pharmacists are not validated, or only internally validated and equates risk-identification and effect of the intervention, e.g. identifying patients at risk of medication related admissions may help to efficiently target preventive interventions.[9–11,21,22] We went one step further in our study, both by stating how the effect of the clinical pharmacist intervention was accounted for by assessing whether there was an interaction between risk group and intervention, and by externally validating the model with an independent cohort.

Similar to our model, comorbidity and previous hospital admissions were important prognostic factors for hospital readmissions in a recently published study, including data from 739 040 patients.[23] The 80 424 patients with a risk of 30 day readmission or death ≥25 % (estimated from the RTCO30D model in Escobar et al.[24]) computed on the day of discharge were followed post-discharge by a transition of care program, resulting in a reduction in 30 day readmission rates.[23]

The main driver of our model was the Charlson comorbidity index score, with increased hazard rates, i.e. decreased time to readmission or death, as expected and supported by the literature.[17,25,26] The Charlson comorbidity index is the most extensively studied index for quantifying an individual's burden of disease and corresponding one year mortality risk.[17,26] However, the original Charlson comorbidity index has been criticised for not sufficiently taking into account age and the diagnoses diabetes, HIV/AIDS, renal disease and cancer.[25] To account for this, age, diabetes, estimated glomerular filtration rate and cancer was among the prognostic factors tested in the development process of our prognostic model. In addition to being included in the Charlson comorbidity index, heart failure was a significant contributor to our model as an independent variable. This emphasizes patients with heart failure as a group with a high risk of readmission or death, which was also an expected finding.[27]

In our study, any previous hospital admissions six months before the index hospital stay was identified as a major risk factor contributing to all-cause readmission or death. The potential sign that patients *without* previous hospital admissions might benefit more from the pharmacist intervention was not replicated in the validation set and was probably a random finding. It nevertheless seems plausible that the healthiest multimorbid patients might benefit most from a pharmaceutical intervention. Accordingly, the baseline analysis of the original RCT showed that patients with a high Charlson comorbidity index score had significantly reduced odds for medication related hospital admissions, suggesting that disease progression rather than medications is the main contributor to hospitalisations in the most complex multimorbid patients.[14] This is also supported by a sub group analysis from a similar randomized controlled trial,[28] were the pharmacist intervention appeared to be more effective in preventing emergency department visits in the patient subgroup using less than five medications.[29] A higher number of medications corresponded to lower levels of medication self-management among patients, and thereby assumingly to less receptiveness for the part of the intervention aimed at improving patient adherence.[29] One explanation to the inconclusive findings in our study might be that the trial inclusion criteria did not select patients most likely to benefit from the intervention.[30] The patients in the derivation set had median 11 regular medications at discharge, supporting the assumption that the healthiest multimorbid patients may have been absent.

The medication related variables, including the number of regular medications at hospital admission, were excluded during the development of our model. Medication factors often fail to account for the appropriateness of medications for the individual patient.[31] Although measures of medication appropriateness, such as Medication Appropriateness Index (MAI) have been found to discriminate between patients at risk of rehospitalisation or mortality, the tools are time consuming and therefore not suitable in clinical practice.[13,31] Furthermore, a potential problem with regards to incorporating a 'number of medications' variable, is the uncertainty of the patient's adherence to the medications, e.g. to a lipid lowering agent.[32] Ultimately, inaccurate medication lists are a common challenge at hospital admission, thus including such variables would require medication reconciliation to be performed before the tool could be used.[33] It might be argued that this would not be the best way to spend limited health care resources.

Number of gene-drug interactions at admission were tested in the model, as an alternative approach to stratifying patients, as a proxy for the risk of harm from medications.[31] This approach could have added user-friendliness to the model, e.g. if the genetic deviation in CYP-metabolizing enzymes were easily accessible in the patient record. No statistically significant prognostic effect of gene-drug interactions was found. Thus, intervention on gene-drug interactions is unlikely to reduce the risk of readmissions in multimorbid patients, although interventions based on gene-drug interactions have recently been reported to prevent adverse drug reaction.[34]

To the best of our knowledge, this is the first study to investigate the *predictive* effect of risk scoring on the effect of a comprehensive clinical pharmacist intervention. In our study, the patients received a comprehensive clinical pharmacist intervention that may have improved their prognosis.[6,15,28,35,36] An effective intervention will typically improve prognosis, and reduce the probability of the outcome.[37] Despite an apparent difference in effect of the intervention between patients previously hospitalised or not, no formally statistically significant interaction was seen, and this subgroup finding was not reproduced in the validation set. In general, few prognostic models are built to differentiate between patient groups with large and small treatment benefits and interaction terms rarely add to the predictive ability of a model.[9,10,20] External validation of Cox models is sparsely treated in the literature (unlike for logistic regression models), and this may be because the validation is not straightforward.[19] However, our results show the importance of external validation as a means to avoid overinterpretation of chance findings.

4.3. Strengths and limitations

The randomised controlled design, the long follow-up of all patients, and the rich data material are factors that strengthen the study. To get the same case mix, the validation cohort was included from the same internal medicines ward with the same inclusion criteria as the randomized controlled trial.[38]

A strength with the present PI, is the small number of variables assigning multimorbid patients to the low, intermediate, or high-risk groups of hospital readmission or death. The one demographic and two clinical variables are clinically relatively readily available, however relying on accurate medical records.[31]

Due to patient safety concerns medication reconciliation should always be conducted when patients are hospitalised. Hence, excluding the 'number of medications' variable in the modelling process could be seen as a limitation of our study.

The study population was limited to the multimorbid patient group, which is a heterogenous group, comprising patients with a variety of diagnoses. Taking into consideration the relatively small size of the validation sample, the small differences in characteristics between the two groups was considered acceptable. However we may in the validation cohort have included a group of a somewhat different composition than the original RCT, which might, on top of a small sample size resulting in wide confidence intervals, to some degree explain the deviations seen.[30] The lack of perfect agreement, visually presented in Fig. 2, may be due to miscalibration as well as random variability due to small sample size. Insufficient power may be one explanation of the non-significant result on the primary outcome in the main study, and the size of the validation set is even more limited. The number of events was 69 (71.1 %) in the validation set, which is lower than the number of events and non-events recommended by Vergouwe et al.[39]

No statistically significant effect of the comprehensive clinical pharmacist intervention on time to first readmission or death was demonstrated in the derivation data set (HR 0.82, 95 % CI 0.64 to 1.04).[15] Nevertheless, it might have proved possible to show better effect in a subgroup of patients.

5. Conclusion

We have developed and externally validated a prognostic model to obtain valid prognosis of readmission and death in patients with multimorbidity. Having a moderate or high Charlson comorbidity index and/or previous admission(s) six months before index stay, and/or heart failure were identified as risk factors of readmissions or death. Knowledge of these variables could aid the detection of at-risk patients.

6. Data availability statement

Deidentified participant data can be made available from the authors on request.

Funding

This work was supported by South-Eastern Norway Regional Health Authority (Ph.D. grant number 12/00718 to author ML). Additional support was provided by the Hospital Pharmacies Enterprise, the University of Oslo, Oslo University Hospital, and Diakonhjemmet hospital. The funding sources had no role in the data collection, analysis or interpretation of the data.

Declaration of interest

None.

CRediT authorship contribution statement

Stine Eidhammer Rognan: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Liv Mathiesen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Marianne Lea:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Morten Mowé:** Writing – review & editing, Project administration, Conceptualization. **Espen Molden:** Writing – review & editing, Conceptualization. **Eva Skovlund:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

Acknowledgements

We thank the people included in the study, the study pharmacists and the hospital ward for facilitating the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2024.06.007.

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