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ORIGINAL ARTICLE

A novel superior medication-based chronic disease score predicted all-cause mortality in independent geriatric cohorts

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Abstract

Objectives: On the basis of current treatment guidelines, we developed and validated a medication-based chronic disease score (medCDS) and tested its association with all-cause mortality of older outpatients.

Study Design and Setting: Considering the most prevalent chronic diseases in the elderly German population, we compiled a list of evidence-based medicines used to treat these disorders. Based on this list, a score (medCDS) was developed to predict mortality using data of a large longitudinal cohort of older outpatients (training sample; MultiCare Cohort Study). By assessing receiver-operating characteristics (ROC) curves, the performance of medCDS was then confirmed in independent cohorts (ESTHER, KORA-Age) of community-dwelling older patients and compared with already existing medication-based scores and a score using selected anatomical-therapeutic-chemical (ATC) codes.

Results: The final medCDS score had an ROC area under the curve (AUC) of 0.73 (95% CI 0.70-0.76). In the validation cohorts, its ROC AUCs were 0.79 (0.76-0.82, KORA-Age) and 0.74 (0.71-0.78, ESTHER), which were superior to already existing medication-based scores (RxRisk, CDS) and scores based on pharmacological ATC code subgroups (ATC3) or age and sex alone (Age&Sex).

Conclusions: A new medCDS, which is based on actual treatment standards, predicts mortality of older outpatients significantly better than already existing scores.

Keywords: Medication-based chronic disease score; Multimorbidity; Risk assessment; Mortality; Elderly

1. Introduction

More than half of all older outpatients suffer from multiple chronic conditions (multimorbidity) [13]. The presence of multiple morbidities is associated with several adverse outcomes such as functional impairment, reduced

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What is new?

Key findings

- In a prospective cohort of older patients with multiple morbidities, a new medication-based, disease-oriented score (medCDS) was developed on the basis of current treatment guidelines for the most prevalent chronic diseases in older patients.
- medCDS is designed to allow easy maintenance and expansion of the score as new and effective medicines become available.
- The score was validated in two independent large longitudinal cohorts of community-dwelling older patients and performed similarly well.

What this adds to what was known?

- In its current form, medCDS performed better than established medication-based scores (e.g. RxRisk or CDS), which are still used for morbidity assessment, and more accurately predicted mortality than an empirical score that used a set of selected anatomical-therapeutic-chemical (ATC) codes or only age and sex.

What is the implication and what should change now?

- medCDS can serve as a tool to compare morbidity-related burden of disease and survival perspectives between different populations and settings (e.g. primary care and public health) whenever morbidity information is incomplete or sparse and treatment information is comprehensive.

quality of life, frequent hospitalization, and increased mortality, health care utilization, and cost [19,21,46]. Applying disease-specific guidelines to patients with multiple morbidities may be inadequate [5,14] because they tend to neglect patient preferences and comorbidities and also because their benefit in patients with multiple morbidities is rarely well established. Hence, instruments to estimate disease burden and associated risks might help identifying patients in need of care and facilitate tailoring of treatment efforts.

To characterize nature and extent of disease burden, to assess its impact on different health outcomes such as mortality, hospitalization, health care utilization, or costs, and also to control confounding by comorbidity in epidemiological studies, it is therefore necessary to measure multimorbidity. In the last 2 decades, several multimorbidity scores have been developed, which are either diagnosis-related or medication-based and help predicting mortality, health care utilization, and quality of life [19,43]. While many but not all (e.g., [47]) of these scores typically also include important cofactors such as age and sex, their assessment of multimorbidity varies; some scores simply count items such as diagnoses or drugs, whereas others differentiate between them, taking into account that not all diagnoses or drugs are equally predictive of an outcome [19]. Theoretically, the performance of such a score can further improve if specific patient details (e.g., drug combinations to account for disease severity) are considered, but, to our knowledge, this has not yet been studied.

Medication-based scores are attractive whenever diagnostic data are not available, inconsistent, or unreliable. In these cases, medication data reflect the currently treated chronic diseases and might have better predictive values and be more reliable, complete, and timely than diagnostic data [11]. Moreover, compared with diagnosis-based chronic disease scores (e.g., the Charlson score [7] or its modifications [34,38]), medication-based scores are robust against underdocumentation of diagnoses or upcoding. However, it has to be acknowledged that not all relevant diseases (e.g., dementia) and geriatric conditions or syndromes (e.g., immobility, frailty, or falls) are sufficiently treatable with drugs and therefore part of the disease burden of a patient may go unrecognized using a medication-based approach. Many of these scores are primarily developed and optimized for the prediction of endpoints other than mortality such as cost [8,12,47] and, therefore, their performance might be worse when used for other purposes. However, also these scores predicted mortality often well [18,19,32,49].

Examples of medication-based multimorbidity indices that are suitable for an analysis of prescription data are the Chronic Disease Score (CDS) [47], RxRisk [12], their modifications and updates (e.g., [8,18,20,36]), and others [39]. These scores link patterns of medication prescriptions with selected chronic diseases. However, in these scores, the selection criteria of diseases are often not transparent (expert opinion) and relevant diseases are missing. Typically, these scores were not specifically developed to predict mortality but rather aimed to estimate cost [8,12,20,47], suggesting that they were not optimized for survival prediction. Moreover, these scores are not kept up to date and a number of drugs are included that are not marketed anymore (e.g., isoproterenol, guanethidine, procainamide, or disopyramide [12,47]), whereas important new pharmacological treatment options with substantial impact on clinical endpoints (e.g., angiotensin II receptor antagonists) or drugs for common chronic conditions (e.g., bisphosphonates for osteoporosis) are missing.

2. Objectives

The aims of this study were to develop and validate a medication-based chronic disease score (medCDS) primarily developed for the prediction of all-cause mortality as a

major and unequivocal clinical endpoint. Furthermore, the medCDS score was compared with different medCDSs which have been used for decades to this end and also with scores assessing influential covariates such as age and sex or numbers of drugs.

3. Methods

3.1. Study design

Considering the most prevalent chronic diseases in the older German population, we compiled a list of evidence-based medicines used to treat these disorders. In an iterative process, this list was refined to best predict the respective diseases. To keep the allocation of diseases to drugs unequivocal, we clustered disorders that are treated with the same compounds. Then a score was developed (medCDS score) to predict mortality using data of a large longitudinal cohort of older ambulatory patients (training sample; MultiCare Cohort Study; [40,42]) and its performance was evaluated in independent cohorts (ESTHER [23,37] and KORA-Age [17]) of older patients (Supplementary Table S1). Concurrently, independent of current treatment guidelines and similar to earlier attempts [6,32,43], we also empirically developed a score (ATC3) based only on pharmacological subgroups of the anatomical-therapeutic-chemical (ATC) codes (3rd level) and assessed its association with mortality. Then, these scores were compared with two previously developed and widely used medication-based morbidity scores (CDS [47] and RxRisk [12]) and also with a score only evaluating age and sex as covariates (Age&-Sex) [44] to define the net contribution of these important variables to mortality in the investigated populations. Finally, for comparison, we also evaluated the performance of the disease-based original [7] and a recently updated Charlson score [34] in the MultiCare Cohort Study and assessed the impact of also considering age and sex in these analyses. The different steps are described in detail in the following.

This study was approved by the Ethics Committee of the Medical Faculty of Heidelberg University, Germany (#S-258/2011).

All steps of the drug selection and coding process were independently performed by at least two health care professionals (pharmacist or physician). If necessary, consensus was reached within a working group consisting of seven pharmacists and physicians.

3.2. Item selection of the medCDS score

The medCDS score focuses on the most common and relevant diagnoses of outpatients and the corresponding medication used in Germany. The target population comprises ambulatory adults aged 65 years or older. The items for the medCDS score were selected in a multilevel process:

In a first step, medical conditions (diseases) with corresponding ICD-10 codes were selected based on the presence of the following criteria: 1) the disease prevalence was $\geq$1% within a standard statutory health insurance data set (GEK) as described by Schäfer et al [41] or within a national cross-sectional study representative for Germany (Bundes-Gesundheitssurvey 1997/98; [4,15]) and 2) diseases must be chronic and continuously treated with specific medication, which is taken on a regular basis.

In a second step, for each selected chronic medical condition, currently effective treatment guidelines were identified by literature search and on the pertinent website of the German Association of the Scientific Medical Societies (AWMF, https://www.awmf.org), and the suggested drug treatment was extracted. Treatment guidelines were considered if 1) they had the highest possible evidence level, 2) were up to date (not older than 5 years), and 3) valid in Germany. If no national guideline was available, another guideline was chosen, preferably European or American. Proposed diagnoses were not included if the medical condition was typically not treated with drugs (e.g., hypotension or diverticulosis).

If a pertinent treatment guideline was identified, all drugs mentioned in it were selected and, if possible, drug groups rather than single substances were chosen. Inclusion criteria for drugs were 1) chronic or regular use (excluding as needed medication), 2) drugs are systemically available (e.g., excluding topical dermatological drugs), 3) used in and by outpatients (exclusion of medication only used in a hospital setting), and 4) the medicines are used for the primary disorder of interest and not for the treatment of comorbidities caused by it. All drugs were linked to the corresponding ATC code.

Subsequently the allocation of drugs (ATC codes) to specific diseases (ICD-10 codes) (candidate predictors) was tested using medication data of the MultiCare Cohort Study [40,42] to detect potential areas of optimization in the drug and disease coding process. Therefore, all ATC codes of patients with a specific disease but without any of the allocated ATC codes were selected to detect potentially missing ATC codes. Conversely, all ICD-10 codes of patients with ATC codes of interest but without suspected underlying ICD-10 codes were selected to detect possibly missing ICD-10 codes.

For the development and application of the score the relationship between each combination of drug and disease must be one to one; hence, whenever the same drug was mentioned in more than one diagnosis,

1) the relationship between drug and corresponding diagnosis was further specified by defining medical conditions predictive of the respective disease (e.g., antidepressants were linked with depression, but whenever antidepressants were given in combination with opioids, the suspected underlying condition was neuropathic pain);
2) diagnoses were combined (e.g., arterial hypertension and heart failure) to one cluster (i.e., cardiovascular diseases), if a drug (class) (e.g., angiotensin-converting enzyme inhibitors) was a current cornerstone of the guidelines of multiple diseases; or

3) the drug was excluded (e.g., if it was unspecific, second line, or off-label medication).

The final selection of medical conditions used for the development of medCDS is shown in Supplementary Table S2.

Within each medical condition of the medCDS, the number of different ATC codes a patient used served as a proxy of disease severity.

3.3. Development and translation of other medication-based chronic disease scores

3.3.1. ATC3 score

We also tested a score counting the number of drugs [6,43] that was based exclusively on ATC codes, age and sex. Therefore, the ATC code of each prescribed drug was truncated to the third level, and the number of different codes was counted (ATC3 score) and used for score development. The final selection of ATC codes used for the development of ATC3 is shown in Supplementary Table S3.

3.3.2. Translation and item selection of CDS and RxRisk

To compare the medCDS score with already existing medCDSs (CDS [47] and RxRisk [12]), we linked drug classes of these scores with the corresponding ATC codes used in medCDS. We used the CDS for comparison because in a previous study, it predicted mortality better [44] than the updated version of the study by Clark et al [8].

3.3.3. Chronic disease score

First we linked all medicines mentioned in the CDS [47] to the corresponding ATC codes (CDS; see Supplementary Table S4). In a second step, we added drug classes recommended in up-to-date treatment guidelines for the mentioned chronic diseases but not mentioned in the CDS (e.g., angiotensin II receptor antagonists for heart disease or proton pump inhibitors for gastric ulcer) yielding a CDS adapted to current treatment standards (updated CDS, see Supplementary Table S5). As suggested in the original publication, this score did not consider age or sex as covariates.

3.3.4. RxRisk

Of all RxRisk classes, we only selected those that are relevant for adults because the medCDS was developed in a setting of older patients. We linked all drugs mentioned in RxRisk with corresponding ATC codes; in ambiguous cases (e.g., RxRisk's category antineoplastics miscellaneous), consensus was reached within the working group (see Supplementary Table S6). As suggested in the original publication, this score considered age or sex as covariates.

3.3.5. Age&Sex

Finally, we also developed a score exclusively based on age and sex of the participants.

3.4. Endpoint definition

Because of its clinical relevance and differences in the length of follow-up of the analyzed cohorts, time to all-cause mortality was chosen as a primary endpoint for score development. In the MultiCare Cohort Study, all deaths of participants were confirmed by the treating general practitioner and/or the relatives of the patients. In ESTHER and KORA-Age, death was ascertained by reviewing the death certificates.

3.5. Study population and setting

The score was developed using data of the MultiCare Cohort Study [40,42]. At the baseline, 3,189 elderly people with multiple morbidities were enrolled between July 2008 and November 2009. The participants were recruited via general practitioners' offices. After 3.75 years and until the end of 2013, the third follow-up assessment was performed. Diseases were documented by the patients' general practitioners and drug information was collected during a visit of a trained scientist or study nurse at the patient homes using a brown-bag medication review method [40]. Of 3,189 patients, 26 did not report any drug intake; the remaining 3,163 patients reported taking altogether 22,973 drugs. Of these, 20,825 drugs (90.6%) could be assigned to an ATC code. The mean number of drugs per patient was 7.3 (median 7, maximum 27). Four patients had no documented survival status and were therefore excluded, leaving 3,159 patients for analysis.

The score performance was tested in two independent cohorts (ESTHER and KORA-Age) of older community-dwelling patients in Germany. The ESTHER population consisted of a subsample of 2,703 participants of the ESTHER study (ESTHER = Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung), a large population-based cohort study conducted in the State of Saarland, Germany [23,37], that initially enrolled 9,949 outpatients aged between 50 and 74 years during a general health checkup by general practitioners between 2000 and 2002 and monitored the patients in follow-ups after 2, 5, 8, 11, and 14 years. The medCDS score was tested in the subsample that received a home visit by a trained study physician during the 8-year follow-up, which took place between July 2008 and December 2010. During this home visit, a comprehensive medication inventory was taken and information on mortality was subsequently collected until March 2013.

The Cooperative Health Research in the Region of Augsburg (KORA)−Age Study is a follow-up study of the four cross-sectional, population-based Multinational Monitoring of Trends and Determinants in Cardiovascular disease MONICA/KORA surveys (S1-S4), carried out between 1984 and 2001 in the region of Augsburg, Southern Germany [17]. Study design, sampling method, and data

Table 1. Medical conditions/disease groups and the corresponding drugs included in the final medCDS score

Disease	ATC name	ATC code	Not considered in the medCDS score, if drug is combined with:
Chronic gastritis, gastroesophageal reflux disease	H_2-receptor antagonists	A02BA	Nonsteroidal antiinflammatory/ antirheumatic drugs (M01A or M01B) because this may rather indicate prophylactic treatment and not the treatment of actual ulcer symptoms.
	Proton pump inhibitors	A02BC	
	Combinations for eradication of Helicobacter pylori	A02BD	
Cardiac arrhythmias	Vitamin K antagonists	B01AA	
	Dabigatran	B01AE07	
	Direct factor Xa inhibitors	B01AF	
	Digitalis glycosides	C01AA	
	Propafenone	C01BC03	
	Flecainide	C01BC04	
	Amiodarone	C01BD01	
	Dronedarone	C01BD07	
	Sotalol	C07AA07	
Asthma, chronic obstructive pulmonary disease (COPD)	Selective beta-2-adrenoreceptor agonists, inhalants	R03AC	
	Adrenergics in combination with corticosteroids or other drugs, excl anticholinergics, inhalants	R03AK	
	Glucocorticoids, inhalants	R03BA	
	Anticholinergics, inhalants	R03BB	
	Antiallergic agents, excl. corticosteroids, inhalants	R03BC	
	Selective beta-2-adrenoreceptor agonists	R03CC	
	Xanthines	R03DA	
	Leukotriene receptor antagonists	R03DC	
	Omalizumab	R03DX05	
	Roflumilast	R03DX07	
Cancer (colorectal, mamma, and prostate carcinoma) including antiemetic therapy	Capecitabine	L01BC06	
	Tegafur, combinations	L01BC53	
	Mistletoe	L01CH01	
		L01CP01	
		L01CP50	
	Lapatinib	L01XE07	
	Everolimus	L01XE10	
	Progestogens	L02AB	
	Gonadotropin-releasing hormone analogs	L02AE	
	Antiestrogens	L02BA	
	Antiandrogens	L02BB	
	Aromatase inhibitors	L02BG	

(*Continued*)

Table 1. Continued

Disease	ATC name	ATC code	Not considered in the medCDS score, if drug is combined with:
	Abiraterone	L02BX03	
	Alizapride	A03FA05	
	Serotonin (5HT3) antagonists	A04AA	
	Aprepitant, fosaprepitant	A04AD12	
Cardiovascular disease category 2 (''heart failure'') CVD2	Ivabradine	C01EB17	
	Sulfonamides, plain	C03CA	
	Aldosterone antagonists	C03DA	
	Furosemide and triamterene	C03EB21	
	Aldosterone antagonists and low-ceiling diuretics	C03EC	
	Aldosterone antagonists and high-ceiling diuretics	C03ED	
Psychiatric diseases including depression, schizophrenia, and anxiety disorders	Non-selective monoamine reuptake inhibitors	N06AA	Opioids (N02A) because combination may rather indicate neuropathic pain[a]; Selective serotonin (5HT1) agonists (N02CC), ergot alkaloids (N02CA01, N02CA02, N02CA51, N02CA52); because combination may rather indicate migraine (only relevant for amitriptyline; N06AA09).
	Selective serotonin reuptake inhibitors (SSRI)	N06AB	Memantine (N06DX01), rivastigmine (N06DA03), donepezil (N06DA02), or galantamine (N06DA04) because combination may rather indicate dementia.
	Monoamine oxidase A inhibitor: moclobemide	N06AG02	
	Monoamine oxidase inhibitor, non-selective: tranylcypromine	N06AF04	
	Serotonin-norepinephrine reuptake inhibitor: venlafaxine	N06AX16	Opioids (N02A), because this may rather indicate neuropathic pain. Selective serotonin (5HT1) agonists (N02CC), ergot alkaloids (N02CA01, N02CA02, N02CA51, N02CA52); because combination may rather indicate migraine.
	Serotonin-norepinephrine reuptake inhibitor: duloxetine	N06AX21	Opioids (N02A), because this may rather indicate neuropathic pain.
	Norepinephrine reuptake inhibitor: reboxetine	N06AX18	
	Noradrenergic and specific serotonergic antidepressant: mianserin	N06AX03	
	Noradrenergic and specific serotonergic antidepressant: mirtazapine	N06AX11	
	Selective noradrenaline and dopamine reuptake inhibitor: bupropion	N06AX12	
	Melatonin receptor agonist: agomelatine	N06AX22	

(*Continued*)

Table 1. Continued

Disease	ATC name	ATC code	Not considered in the medCDS score, if drug is combined with:
	Trazodone	N06AX05	
	Hypericum perforatum	N06AP01	
		N06AP51	
		N05CP03	
	Benzodiazepine derivatives (anxiolytics)	N05BA	
	Antipsychotics	N05A	Memantine (N06DX01), rivastigmine (N06DA03), donepezil (N06DA02), or galantamine (N06DA04) because this may rather indicate dementia[b].

[a] Only relevant for desipramine (N06AA01), imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), maprotiline (N06AA21), doxepin (N06AA12), venlafaxine (N06AX16), and duloxetine (N06AX21).

[b] Only relevant for citalopram (N06AB04), risperidone (N05AX08), olanzapine (N05AH03), haloperidol (N05AD01), melperone (N05AD03), quetiapine (N05AH04), pipamperone (N05AD05), and aripiprazole (N05AX12).

collection have been previously reported in detail [33]. In brief, between November 2008 and November 2009, a self-administered questionnaire was sent to all S1-S4 participants born before 1944 (aged $\geq$ 65 years), in which information about drug consumption of the last 7 days, prescribing status, and administration regimen were gathered including the unique package codes used in Germany (Pharmazentralnummer). The pharmaceutical products were classified according to their active ingredients following the ATC classification system. For the present analysis, only regularly consumed drugs prescribed or advised by a physician were included. Approximately 16,000 preparations were reported. In 2011, a mortality follow-up of the KORA-Age population was conducted. Vital status was ascertained by the registration offices. Follow-up time was calculated from the date of answering the questionnaire to the last date confirmed of being alive or dead, or the last date of registration in case of leaving the catchment area or unknown vital status, whichever came first (median follow-up 2.53 years). Altogether 4,127 participants of KORA-Age were included in this analysis.

3.6. Score development and statistical analysis

Multivariate Cox proportional hazard regression was applied to assess the influence of the candidate predictors in the time until death in the MultiCare Cohort Study used as the training sample. A backward stepwise selection of variables based on the Schwarz Bayesian information criterion (BIC) was applied to reduce overfitting. The BIC penalizes the log likelihood of a model (a measure of its fit) by a factor related to the number of predictor variables in the model (a measure of its complexity) and the number of cases. A reduction of BIC indicates model improvement. To derive a simplified score, the β coefficients of the final model were transformed into integer score points by dividing through the lowest β coefficient and rounding. The medCDS score was calculated as the sum of these score points. The upper decile and the upper quintile of the score were used to define the cut-points for the corresponding risk groups (low–medium–high risk). The cumulative hazard rates for the respective risk groups were calculated using the Kaplan-Meier method.

For validation, the predictive accuracy of the medCDS score was assessed in the independent cohorts ESTHER and KORA-Age.

To assess the discrimination of the score, the receiver-operating characteristics (ROC), the area under the ROC curve (AUC), its 95% confidence interval (95% CI), and c-statistics were calculated. The discrimination was then compared with the other medCDSs (CDS, the updated CDS, RxRisk, Age&Sex, and ATC3).

The score development of the ATC-based score (ATC3) was similar and applied a Cox proportional hazard regression model with backward stepwise selection based on the BIC. The score based on age and sex (Age&Sex) was derived by applying a Cox proportional hazard regression model with age and sex as predictors and by using the rounded β coefficients as score points. The final score was derived by dividing the β coefficients through the lowest β coefficient and rounding.

For the statistical analyses and the score development, SAS Version 9.3 was applied.

4. Results

After linking with drugs and clustering, 28 medical conditions remained and were used for score development (Supplementary Table S2). It was assumed that a patient suffers from a condition, if at least one of the corresponding drugs was taken. Altogether six of 28 medical conditions as

well as age and sex were significantly associated with mortality (Table 1) and thus included in the final medCDS. The estimated β coefficients, the hazard risk ratios, the 95% CI, and the derived score points are shown in Table 2. All corresponding medicines of these diagnosis groups are listed in Table 1. Aside from age, cancer and heart failure (cardiovascular disease category 2) were associated with the highest mortality risk (3 points each) (Table 2).

The maximum attainable sum of the score points of the final medCDS score was 16, the maximum observed in the training cohort was 14 points, and the corresponding ROC AUC was 0.73 (95% CI 0.70-0.76) (Table 3). The clustering of the patients into the three risk groups (low, medium, and high) is shown in Supplementary Table S7. The consideration of the number of drugs within a disease group as a proxy for disease severity rather reduced than increased the performance of the medCDS (ROC AUC 0.70; 95% CI 0.67-0.74; Fig. 1).

The risk groups were defined using the upper quintile and the upper decile of the score; this led to the cut-points $\leq$ 5 points (low risk), 6 points (medium risk), and $\geq$7 points (high risk). The corresponding Kaplan-Meier curves are presented in Fig. 2. The Log rank test shows a highly significant difference between the risk groups in the MultiCare Cohort Study ($P < 0.001$; Fig. 2).

In the validation cohort KORA-Age, the ROC AUC of the medCDS was 0.79 (95% CI 0.76-0.82; Fig. 3). The difference between the risk groups regarding survival is highly significant ($P < 0.001$, log rank test; Fig. 4).The ROC curves of the validation in the ESTHER cohort are shown in Fig. 5, their ROC AUC values are reported in Table 3, the corresponding Kaplan-Meier curves show a highly significant difference ($P < 0.001$, log rank test; Fig. 6).

The performance of the medCDS was superior to the already existing medication-based scores RxRisk and CDS. Updating of the CDS with drugs missing according to current treatment guidelines did not improve its performance

Table 2. Cox regression model of the final medCDS as established in the MultiCare Cohort Study

Parameter	β coefficients	*P*	HR	95% CI	Score points
Sex					
Female	0		1		0
Male	0.41666	0.0006	1.517	1.198–1.921	1
Age (y)					
<75	0		1		0
75–<85	0.75689	<0.0001	2.132	1.662–2.734	2
≥85	1.66119	<0.0001	5.266	3.133–8.849	5
Cancer (colorectal, breast, and prostate carcinoma) including antiemetic therapy					
No	0		1		0
Yes	1.15605	<0.0001	3.177	1.879–5.374	3
Cardiac arrhythmias					
No	0		1		0
Yes	0.46329	0.0005	1.589	1.223–2.065	1
Asthma/COPD					
No	0		1		0
Yes	0.39064	0.0078	1.478	1.108–1.971	1
Chronic gastritis, gastroesophageal reflux disease					
No	0		1		0
Yes	0.49017	0.0005	1.633	1.239–2.151	1
Cardiovascular disease category 2 (CVD2) (“heart failure”)					
No	0		1		0
Yes	0.92391	<0.0001	2.519	1.960–3.238	3
Psychiatric diseases including depression, schizophrenia, and anxiety disorders					
No	0		1		0
Yes	0.36834	0.0131	1.445	1.080–1.934	1

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

Table 3. Comparative assessment of the performance of different scores expressed as ROC AUC (95% CI; Harrell's C-statistic)

Cohort	medCDS	ATC3	CDS
Score development			
MultiCare	0.730 (0.699-0.761; 0.729)	0.706 (0.674-0.739; 0.710)	0.657 (0.623-0.691; 0.653)
Score validation			
KORA-Age	0.788 (0.759-0.817; 0.783)	0.777 (0.747-0.807; 0771)	0.641 (0.603-0.679; 0.636)
ESTHER	0.743 (0.708-0.778; 0.731)	0.724 (0.687-0.761; 0.715)	0.657 (0.619-0.696; 0.655)

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC, receiver-operating characteristics.

(Table 3). The performance of the medCDS was better than the simple score based on pharmacological subgroups of the ATC code (ATC3) ($P = 0.022$) (Table 3). In all analyses, the score merely considering age and sex (Age&Sex) performed worse than medCDS and ATC3.

The c-statistics of the original Charlson score in the MultiCare Cohort Study was 0.6190 and, considering also age and sex, 0.6911; the respective values for the updated Charlson score were 0.6142 and 0.6884, thus predicting mortality significantly less well than medCDS.

5. Discussion

The newly developed medCDS score, which is based on current treatment guidelines, more reliably predicts mortality than the already established medCDSs CDS and RxRisk, which are still used for morbidity assessment [10,29]. Its validity was confirmed in two independent cohorts of ambulatory older persons, and medCDS was even superior to the CDS when the CDS was updated to reflect current evidence-based treatment guidelines.

The performance of the simple score that included ATC codes (ATC3) was almost as good as the performance of the more complex medCDS. Similar observations were made by several groups which demonstrated that simple counts of medications may perform better than more complex measures in predicting health care costs and utilization as endpoint [6,32,43].

We established and validated the medCDS score in three large cohorts with rather exhaustive information on current drug therapy because in these studies, drug histories were either taken at a home visit using a technique similar to the brown-bag review procedure (MultiCare, ESTHER) or information was collected in a questionnaire survey asking for unique package code information of all drugs (KORA-Age) [35]. medCDS was therefore developed and optimized in a setting with rather comprehensive and unequivocal drug information, and its predictive power will thus be best if the amount and depth of information is comparable with the information considered during score development.

Another important prerequisite defining the predictability of medication-based scores is that the drugs are used consistently in the respective population and that they are

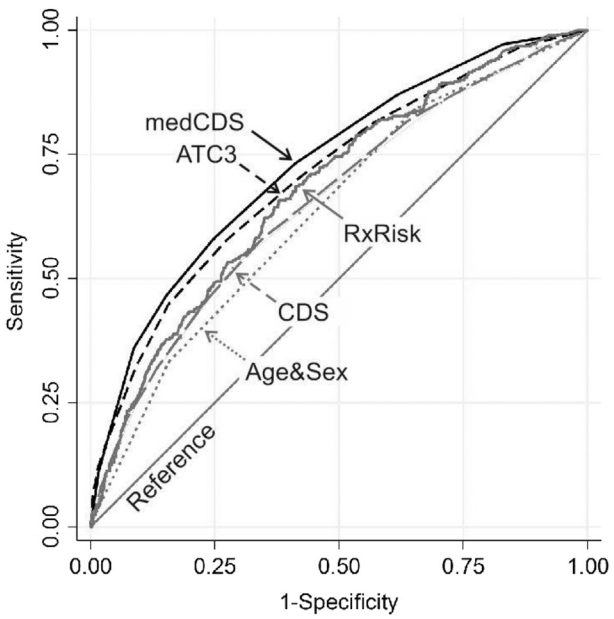

Fig. 1. Results obtained in the training sample using the MultiCare Cohort Study: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

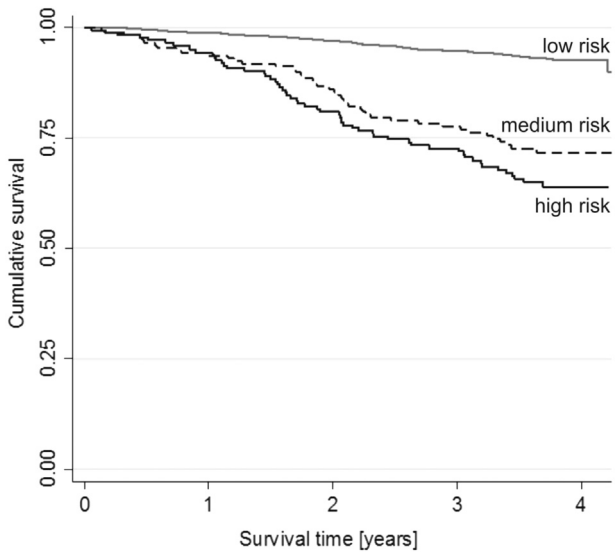

Fig. 2. Performance of the training sample MultiCare Cohort Study: Kaplan-Meier curves of the different risk groups.

Updated CDS	RxRisk	Age&Sex
Score development		
0.653 (0.618-0.687; 0.651)	0.681 (0.649-0.713; 0.681)	0.637 (0.604-0.670; 0.637)
Score validation		
0.624 (0.585-0.662; 0.619)	0.702 (0.669-0.736; 0.697)	0.732 (0.698-0.766; 0.725)
0.642 (0.601-0.682; 0.637)	0.700 (0.664-0.737; 0.695)	0.658 (0.618-0.697; 0.653)

allocated to only one risk group. A number of drugs are approved for different conditions (e.g., angiotensin-converting enzyme inhibitors), and the endpoint of interest (e.g., mortality) can vary between indications (e.g., heart failure and hypertension), which can limit the performance of scores using this information. In addition, drugs can also be used outside the labeled indications, incorrectly dosed, or may not be taken at all. Therefore, these scores will never be perfect and always require updating when new indications with relevant impact on the endpoint of interest emerge. In theory, ambiguities arising when drugs are approved for indications with differing risk profiles can be resolved by considering also medical conditions in the score. Several scores have successfully combined information on diseases and medication in the past, which helped avoid undercoding and often improved the predictive power (e.g., [1,25]). Whether medCDS will also improve if it is combined with medical conditions will have to be assessed.

Not all initially selected chronic medical conditions significantly predicted mortality; not surprisingly, the mortality risk was highest in patients with medications for the treatment of cancer and heart failure whose association with high mortality rates is well established [9,45]. The risk was also increased in patients using medications for ulcer, psychiatric diseases, asthma/chronic obstructive pulmonary disease (COPD), and arrhythmia, confirming the results of epidemiological studies showing an increased mortality risk for gastroesophageal reflux disease patients in the general population as well as for patients suffering from COPD, arrhythmia, or psychiatric diseases such as depression [2,24,30,31]. However, other diseases that are clearly associated with increased mortality such as Parkinson's disease [48] were not predictive and thus not selected in the final score. This may be due to fact that the prevalence of patients with Parkinson's disease was very low in the MultiCare Cohort Study (2.1% of all patients), which was used for score development. In addition, drugs used in the treatment of cardiovascular and cerebrovascular disease such as platelet aggregation inhibitors or anticoagulants (prevalence in MultiCare: 52.3%) or lipid-lowering drugs (42.4%) were not indicators of mortality in our assessment albeit their high prevalence in the MultiCare Cohort. The reasons for the poor prediction of mortality by these medicines are unknown but numerous factors may have influenced such a result. (1) Accurate prediction of mortality risk by a medication-based score depends on the effectiveness of the respective treatment in preventing disease-

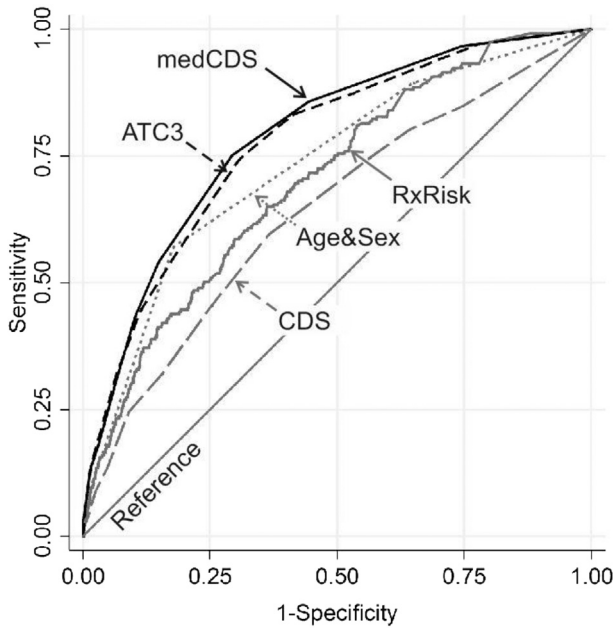

Fig. 3. Results obtained in the validation cohort KORA-Age: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

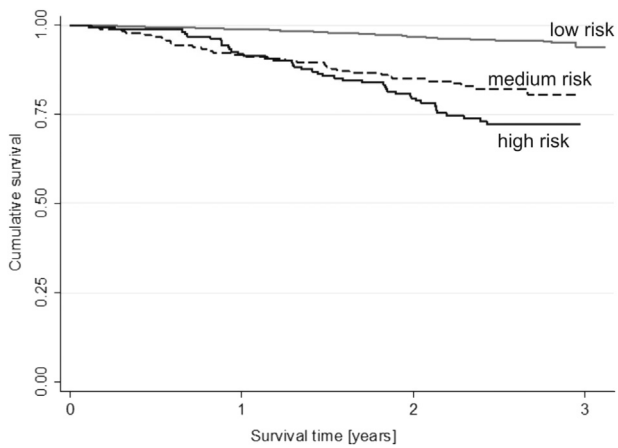

Fig. 4. Performance of the validation cohort KORA-Age: Kaplan-Meier curves of the different risk groups.

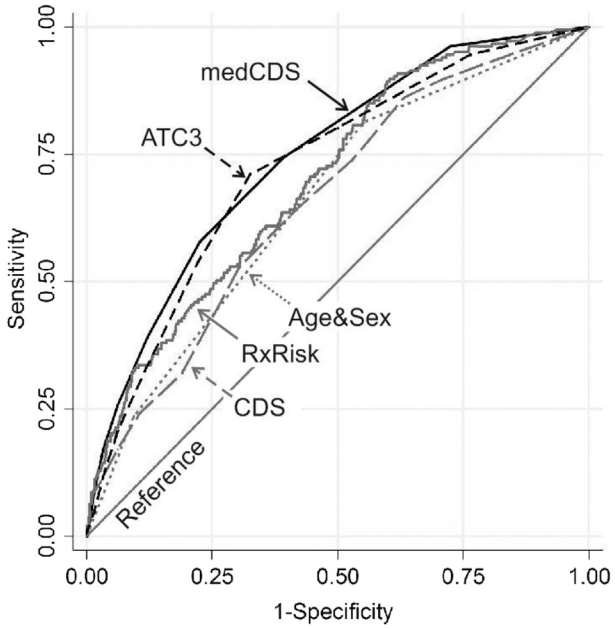

Fig. 5. Results obtained in the validation cohort ESTHER: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

related death. Hence, the better the treatment works, the more difficult it becomes to detect a mortality difference to patients having other diseases or even no disease. (2) Mortality also depends on the available therapeutic alternatives and their effectiveness if drug treatment fails, which means that for coronary heart disease patients on aspirin and lipid-lowering drugs effective alternatives (e.g., cardiac interventions in acute coronary syndromes) are available in emergency situations. Finally, (3) even in advanced stages of coronary heart disease [16], 5-year mortality rates are manifold lower than in patients with heart failure [27], making it difficult to detect corresponding signals in relatively small cohorts and short follow-up periods.

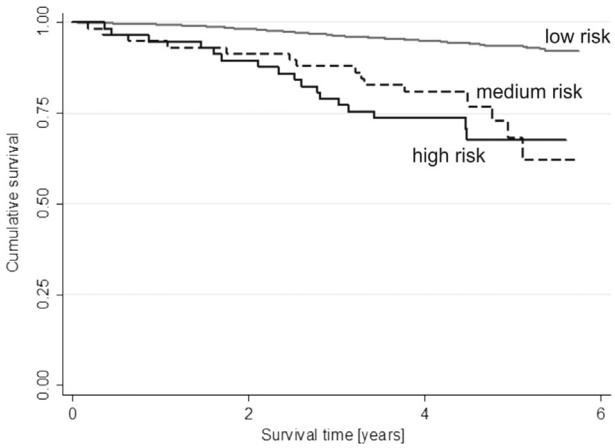

Fig. 6. Performance of the validation cohort ESTHER: Kaplan-Meier curves of the different risk groups.

5.1. Limitations and strengths of the medCDS score

The medCDS score was developed to predict all-cause mortality and was based on the MultiCare Cohort, which had a follow-up period of 3.75 years. Its validation was performed in two independent cohorts of ambulatory patients with a comparable length of follow-up. While the score performed at least equally well in the confirmatory analyses, these assessments cannot prove that medCDS will also be able to predict longer term mortality. Moreover, other important endpoints such as quality of life or health care services utilization (e.g., hospitalization), which also have an important impact on the health care system, have not yet been studied. It is thus open whether the medCDS will predict other endpoints as well and whether the score will require adaptation of the medical conditions and weights. However, previous experiences with medication-based scores clearly indicate that not all scores predict all endpoints similarly well, suggesting that the medCDS score may also require adaptation [19,32,47]. Similarly unknown is whether the performances of ATC3 and medCDS scores will differ more from each other when other endpoints are considered.

We included common chronic diseases of outpatients that are treated with drugs. However, other diseases and drugs may also be associated with mortality; pertinent examples are i) conditions that are not treated with drugs in ambulatory care (e.g., obesity, renal dysfunction), ii) acute events (e.g., stroke), iii) treatments that are only applied in hospitals and may have long-lasting effects (e.g., parenteral antineoplastic agents), or iv) rare diseases with significant mortality that are too rare to meet the inclusion criterion of 1% prevalence (e.g., pancreatic cancer). This may become more relevant if larger cohorts with more diverse populations such as general health insurance data will be evaluated.

For the allocation of drugs to diseases, we primarily used the German summary of product characteristics (drug label) and guidelines approved in Germany because all evaluated cohorts were established in Germany. It is well known that guidelines can differ across different countries and continents (e.g., with respect to specific treatment goals [28]), but the sole allocation of drugs to diseases is likely less sensitive to such differences and transferability of the results appears thus not limited.

Moreover, medication underuse, which is common in ambulatory care, is associated with poorer outcomes [3], and was also frequent in one of the included cohorts (ESTHER [26]). Because the medCDS is medication-based and independent of diagnostic criteria and coding, it will fail to detect patients not treated with indicated drugs, which may lead to misclassification and reduce the prediction of the score. In addition, medication-based scores will neither be suitable to detect medication misuse (e.g., inappropriately dosed drugs), which can result in both toxicity and nonresponse. However,

because the accuracy of diagnosis codes has also been frequently questioned, medication data are nevertheless considered reliable alternatives [11,22]. However, as shown in this analysis, medCDS can serve as a tool to compare morbidity-related burden of disease between different populations and settings (e.g., primary care and public health).

There are also several strengths of the introduced medCDS score. To be as comprehensive as possible, all common chronic diseases of outpatients that are treated with drugs were considered when developing the score. However, to simplify score application, we included only medical treatments in the final medCDS score with a significant impact on the primary outcome. The medCDS focuses on mortality, which is a major clinical endpoint. In an ambulatory setting, the medCDS score is superior to already existing medication-based scores such as CDS and RxRisk even when they are updated to match current treatment standards of the diseases considered therein. Moreover, its high external validity shows its robustness and immediate applicability to other ambulatory cohorts.

6. Conclusion

In conclusion, based on current treatment guidelines for the most prevalent chronic diseases in older outpatients, we developed a medCDS that predicts mortality of ambulatory patients better than already existing scores (CDS and RxRisk) and confirmed its validity in two independent large longitudinal cohorts of older patients (KORA-Age, ESTHER). While in its current form, the medCDS well predicted the mortality risk of independent populations, further research is now needed to adapt the medCDS to other relevant outcomes, for example, (avoidable) hospitalization, health care services utilization, quality of life, or limitations in activities of daily living. Moreover, also this score will require periodic updating as science progresses.

Conflict of interest statement

None.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2018.09.004.

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