BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021122
Article Type:	Research
Date Submitted by the Author:	12-Dec-2017
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Keywords:	chronic disease burden, comorbidity, mortality prediction, model validation, claims data, weighting

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Key words: chronic disease burden, claims data, comorbidity, weighting, mortality prediction, model validation.

Word Count: 2819

Abstract (300 words allowed)

Objectives: To validate the Rx-Risk comorbidity index for medicines mapped to the Anatomical Therapeutic Chemical (ATC) classification system codes.

Design: The 46 comorbidities in the Rx-Risk index were mapped to dispensing's indicative of each condition using ATC codes. Prescription dispensing claims in 2014 were used to calculate the Rx-Risk. A baseline logistic regression model was fitted using age and gender as covariates. Rx-risk was added to the base model as an (i) unweighted score, (ii) weighted score, and as (iii) individual comorbidity categories indicating the presence or absence of each condition. The Akaike information criterion (AIC) and c-statistic were used to compare the models.

Setting: Models were developed in the Australian Government Department of Veterans' Affairs health claims data and external validation was undertaken in a 10% sample of the Australian Pharmaceutical Benefits Scheme Data.

Participants: Subjects aged 65 years or older

Outcome measures: Death within one year (eg 2015)

Results: Compared to the base model (c-statistic 0.738, 95% Confidence Interval (CI) 0.734-0.742), including Rx-Risk improved prediction of mortality; unweighted score 0.751, 95%CI 0.747-0.754, weighted score 0.786, 95%CI 0.782-0.789 and individual comorbidities 0.791, 95%CI 0.788-0.795. External validation confirmed the utility of the weighted index (c-statistic=0.833).

Conclusions: Rx-Risk strongly predicted one-year mortality, however, modelling Rx-Risk as individual covariates may be most useful in practice.

Strength and Limitations of this study (5 bullet points that relate to methods. No results)

Strengths

- This study provides an up to date list of medicines identified by ATC codes mapped to individual Rx-Risk categories
- Rx-Risk mapped to ATC codes can be easily adapted for use in other health systems making this index a useful resource for researchers worldwide

Limitations

- The Rx-Risk index has been updated and mapped to ATC codes based on medicine availability in Australia; hence modifications may be required for use in other health systems
- This study was limited to patients over 65 years of age so Rx-Risk category weights derived in this study may not be applicable to younger populations.

Introduction

The prevalence of multi-morbidity in the population is increasing [1, 2] and patients with multiple conditions are at greater risk of adverse outcomes [3]. In observational studies in which the aim is to determine the association between medicine use and adverse events, adjustment for multi-morbidity is required to avoid biased results. Reliable methods for identifying and controlling for multiple comorbidities are required in order to make valid comparisons between treatments. The Rx-Risk is a measure for determining an individual's current comorbidities based on their prescription medicine dispensing [4, 5]. It was initially developed for predicting costs of health care [6] and was subsequently adapted to predict mortality in outpatient populations [7, 8]. Rx-Risk has been found to be a better predictor of one- and three-year mortality (one-year mortality: weighted Rx-Risk c-statistic=0.728, 95% CI=0.723-0.733, three-year mortality: 0.731, 95%CI=0.728-0.734) compared to simple prescription counts in the same time periods (one-year mortality: 0.715, 95%CI=0.710-0.720, three-year mortality: 0.718, 95%CI=0.715- 0.721) [9].

The first pharmacy based measure of comorbidity, developed in 1992, was The Chronic Disease Score (CDS) [4], consisting of 17 comorbidity categories. The CDS was subsequently updated and renamed in 2003 as the Rx-Risk-V index, consisting of 45 categories of comorbidity [10]. The Rx-Risk-V index was then adapted to only include comorbidities for which a medicine could be prescribed and therefore could be applied to prescription claims data resulting in an index based on 42 categories of comorbidity [11]. Due to continual advances in pharmaceutical disease management and as new medicines are used to treat particular diseases, e.g. treatment for hepatitis B and C, the Rx-Risk requires periodical updating and re-validation. A list of Rx-Risk comorbidities and their corresponding medicines

mapped to a standardised international coding system would facilitate use of the index across health systems. Other comorbidity scores such as the Elixhauser and Charlson Index [12, 13] require diagnostic information in their construction. The advantage of the RxRisk is that it requires prescription data only and provides researchers with the ability to measure comorbidity even in a predominately outpatient setting.

To facilitate the use of the RxRisk in practice, this paper provides a list of the individual RxRisk categories mapped, using clinical expertise, to the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system [14]. The aim of this study was to determine the validity of the Rx-Risk index, in predicting one-year mortality in an outpatient population.

Method

Rx-Risk index mapping

The Rx-Risk index consists of 46 comorbidity categories. For each Rx-Risk category, medicines indicative of that condition were mapped (see Table 1). This mapping was performed at the ATC classification level and performed by consensus between two pharmacists. If an individual had ≥1 dispensing for a medicine in a given category then they were considered to have been treated (using medicines) for that comorbidity.

Data sources

The primary data source was the Australian Government Department of Veterans' Affairs (DVA's) administrative claims database. This database contains details of all prescription medicines, medical and allied health services, and hospitalisations subsidised by DVA. The

current treatment population consists of 223,181 members of the Australian veteran community, which includes veterans, war widows and widowers. The median age of the DVA treatment population is 75 years and 62% are men. DVA also maintains a client file containing gender, date of birth and date of death information.

External validation of the Rx-Risk index was conducted using the Pharmaceutical Benefits Scheme (PBS) 10% sample of the Australian population. This dataset contains information on the dispensing of prescription medicines, and includes basic demographic information regarding gender, year of birth and year of death. It is maintained by the Australian Government Department of Human Services. The current treatment population consists of 1,346,340 members of the Australian community. The median age of the PBS treatment population is 43 years and 48% are men.

Medications in both the DVA and PBS datasets are coded using the World Health Organisation anatomical therapeutic chemical (ATC) classification system [14] and PBS item codes [15].

Study population

The DVA study population included individuals with at least one health care encounter in the six month period from 1 July 2013 to 31 December 2013. A health care encounter included any of the following: a medication dispensing, a doctor's visit, or hospitalisation. Analysis was restricted to veterans who were DVA Gold Card holders prior to 1 July 2013 (ensuring they were eligible for all DVA subsidised services, thus the data set captured all their health claims), and were between the ages of 65 and 100 years at 1 January 2015 (N=135,406). Inclusion criteria for the PBS cohort were people with a health care encounter (defined as at least one medicine dispensing) in the six month period from 1 July 2013 to 31 December 2013, who were aged between 65 and 100 years at 1 January 2015 (N=303,135).

The primary outcome for this study was death recorded in 2015. Rx-Risk scores were calculated separately in each dataset over a one-year baseline period (1 January 2014 – 31 December 2014).

Calculating Rx-Risk scores and prescription counts

The full Rx-Risk index has 46 comorbidity categories; however, tuberculosis, and hepatitis B and C were removed from the Rx-Risk index for this study as the number of individuals with these conditions in the DVA cohort was less than 10 so weights could not be generated. This resulted in 43 categories in the validation study. The following forms of the Rx-Risk score were generated. The unweighted Rx-Risk score was calculated as the count of the number of different comorbidity categories for which an individual was treated with a possible score ranging from 0 to 43. The weighted Rx-Risk score was calculated by adding the 43 indicator variables to a logistic regression model with mortality as the outcome and age and gender as predictors. From this model each comorbidity was assigned a weight according to the statistical significance and magnitude of the resulting odds ratio (Table 2)[7]. The weighted Rx-Risk score for an individual was then the sum of the weighted indicator variables.

[Insert Table 2 here]

Three crude prescription counts were also calculated: (i) total number of prescriptions dispensed in the baseline period (1 January 2014 – 31 December 2014), (ii) total number of unique medicines dispensed in the baseline period based on ATC codes, and (iii) total number of unique medicines dispensed during the baseline period based on PBS item codes[15]. The distinction between ATC and PBS codes was made because different strengths or formulations of the same medicine have the same ATC code but different PBS codes; e.g. if a patient is dispensed two different strengths of the same medicine, this will be

counted once in the total number of ATC medicines dispensed but twice in the total number of PBS medicines dispensed.

Statistical analysis

Primary analysis was performed in the DVA database. A baseline logistic regression model was calculated for mortality using age and gender as predictors. The comorbidity scores, individual comorbidities, and crude prescription counts were added to the baseline model separately. Age, comorbidity scores and crude prescription measures were included in the models as continuous variables assuming linear associations. The overall goodness-of-fit of each model was compared to the baseline model using the Akaike Information criterion (AIC)[16]. The model with the lowest AIC value is considered the best fit. The difference between the AIC values of two models must be greater than 10 for one model to be considered superior to the other. Model discrimination was compared based on the c-statistic and the relative Integrated Discrimination Improvement (IDI) [17]. The value of the c-statistic can range from 0 to 1, with 1 indicating perfect prediction and 0.5 indicating chance predictions. A c-statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable[18]. Using 1000 bootstrap samples 95% confidence intervals were calculated for the c-statistics[9].

Internal validation of weighted scores

We used 10-fold cross-validation to internally validate the binary logistic regression model used to calculate the Rx-Risk category weights. This subsets the DVA cohort, using random sampling without replacement, into 10 equal folds. Each fold is a 10% subset of the DVA cohort. The training set consisted of 9 folds and was used to calculate Rx-Risk category

weights. The calculated weights were then applied to the testing set (i.e. fold left out of training set). A binary logistic regression model of one- year mortality including age, gender and weighted Rx-Risk was built separately for the training set and testing set and the c-statistics recorded. This process was repeated ten times until each fold was used as the testing set once. This resulted in 20 c-statistics being calculated, 10 each on the training and testing set. The average c-statistic was recorded for each set.

Two sensitivity analyses were carried out. In the first sensitivity analysis we used the lower confidence limit of the odds ratio to determine the Rx-Risk category weights rather than the estimated odds ratio itself. We did this as some comorbidities are uncommon in this population resulting in large confidence intervals. In the second sensitivity analysis we calculated the Rx-Risk category weights (based on the odds ratio) generated from 5000 bootstrap samples. For each Rx-Risk category the weight was calculated as the median of the 5000 weights for that category generated in each bootstrap sample. We did this sensitivity analysis to test the stability of the weights.

External Validation

Using the same methods described above we also derived Rx-Risk category weights in the PBS data and compared them to the base model in this dataset. Additionally, we compared unweighted scores, individual Rx-Risk categories, and crude prescription counts to the base model. To determine the external validity of the weights, the calculated Rx-Risk category weights derived from the DVA dataset were applied to the PBS cohort, and vice versa. The Akaike information criterion model fit and c-statistics were calculated to determine the validity of the models.

Results

Table 1 presents the ATC mapped Rx-Risk categories, derived empirical weights, and number of treated individuals within the DVA and PBS populations. The most frequent comorbidities identified by the Rx-Risk index in the DVA cohort were hypertension (53%), gastro-oesophageal reflux disease (GORD) (51%), hyperlipidaemia (50%), and conditions treated with antiplatelets (39%). In the DVA cohort of 135,406 people, with an average age of 83 years (standard deviation (SD) 9.5) and 47% were men. The median unweighted Rx-Risk score was 5 (interquartile range (IQR) 3-7) and the median weighted Rx-Risk score was 3 (0-6).

The baseline model, comprising only age and gender, predicted one-year mortality moderately well in the DVA cohort (c-statistic=0.738, 95% Confidence Interval (CI) 0.734-0.742). The addition of Rx-Risk to the model increased the performance of the model: unweighted Rx-Risk c-statistic=0.751, (95% CI 0.747-0.754), IDI=14.0%, p-value<.0001; weighted Rx-Risk c-statistic=0.786, (95% CI=0.782-0.789), IDI=65.6%, p-value<.0001; 43 individual comorbidities c-statistic=0.791, (95% CI=0.788-0.795), IDI=73.9%, p-value<.0001. The model including the 43 comorbidity indicator variables had the lowest AIC (75692), highest c-statistic (0.791), and the highest discrimination improvement (73.9%). The models including the weighted Rx-Risk score or 43 comorbidity measures were better predictors of one-year mortality than any of the crude prescription measures (Table 3). Results of the internal 10-fold cross validation were consistent with the main analysis with an average c-statistic of 0.785 achieved over the 10 testing datasets compared to a c-statistic of 0.786 in the primary analysis.

[Insert Table 3 here]

In the sensitivity analysis using the lower 95% confidence interval limit in the weighting algorithm we found a very similar performance with a c-statistic of 0.787 compared to the weighting algorithm using the estimated odds ratio (c-statistic 0.786). In the second sensitivity analysis in which the weights were calculated from 5000 bootstrap samples we found a similar c-statistic (0.786) compared to the primary analysis.

The PBS cohort consisted of 303,135 people, with an average age of 75 years (standard deviation (SD) 7.4) and 45% were men. Similar to the DVA cohort, the most frequent comorbidities identified by the Rx-Risk index in the PBS cohort were hypertension (54%), hyperlipidaemia (52%) and gastro-oesophageal reflux disease (GORD) (41%). The median unweighted Rx-risk score was 4 (2-6) and the median weighted Rx-Risk score was 3 (0-7). When the DVA derived Rx-risk category weights were applied to the PBS population we found a c-statistic of 0.833 (Table 3).

Compared to the base model including just age and gender in the PBS population (c-statistic 0.761), the Rx-Risk index treated as individual covariates was most predictive of one-year mortality in this cohort (c-statistic= 0.845, (95% CI 0.842-0.849), IDI=114.8%, p-value<.0001) and performed better than all other forms of the Rx-Risk score.

Discussion

This paper presents the Rx-Risk index with each comorbidity category mapped to medicines at the ATC classification level using clinical expertise. The mapped index provides a resource for researchers working with health claims data utilising ATC codes or that have mappings to

the ATC codes to calculate comorbidity, based on prescription medicine dispensing's in an outpatient population. We have shown that the updated Rx-Risk was highly predictive of one-year mortality in both the populations examined and is a valid measure of comorbidity in an outpatient population and is therefore likely to be useful in a range of observational data settings.

All forms of Rx-Risk predicted mortality better than just age and sex alone. The best results for predicting one-year mortality were achieved when modelling Rx-Risk as individual comorbidities or as a weighted score. The unweighted Rx-Risk score had similar performance to simple prescription medicine counts. In practice, Rx-Risk treated as individual covariates may be more easily applied, however, the weighted score may be a better option when sample sizes are smaller taking up fewer degrees of freedom. Making the ATC map available to researchers will facilitate the use of the Rx-Risk in place of comorbidity estimated simply by prescription counts.

Internal and external validation showed that the weighted index was predictive of one-year mortality within different subsets of the veteran population and in a general population and is likely to be generalizable to other elderly populations.

The Rx-Risk index has been updated accounting for the introduction of new medicines to the market, making this index a useful resource for researchers. The updated Rx-Risk has 46 comorbidities, however 3 (tuberculosis, and hepatitis B and C) were removed in the analysis stage as there were insufficient cases in the DVA cohort. A younger or larger sample may have allowed these comorbidities to be assessed. For consistency, these comorbidities were also excluded from the analysis in the PBS cohort despite there being few but sufficient cases. The Rx-Risk index has been updated and mapped to ATC codes based on medicine

availability in Australia; hence modifications may be required for use in other health systems.

The health care encounter inclusion criteria were not the same for both cohorts. The DVA cohort included people with a hospitalisation or GP visit, while the PBS cohort was limited to those with a prescription dispensing only. However, the difference across populations is small, as 96.7% of the DVA cohort had a medication dispensed in the six month selection period.

Including all individual comorbidities as indicator variables may not be appropriate in some studies, such as those looking at the effect of a particular treatment on an adverse event when the treatment itself is included in the construction of the comorbidity score. For example, when determining whether the risk of NSAIDS is associated with gastrointestinal bleeds, it would not be correct to adjust for inflammation/pain as an indicator as the medicines mapped to this comorbidity include NSAIDs. In this scenario it would be advisable to remove inflammation/pain as an indicator or use the weighted Rx-Risk score. Lastly, the Rx-Risk category weights derived in this study may not be applicable to younger populations. We limited our cohorts to patients over 65 years of age so factors that are predictors of mortality in this age group may not be predictors in a younger group. When we applied the weights derived in the veteran population to the 10% Australian PBS sample the predictive model had a c-statistic of 0.833 which was higher than the c-statistic calculated when weights were derived on the 10% sample itself (c-statistic=0.809) but not as good as using the individual comorbidity indicators. We suggest the reason for the lower c-statistic when using PBS weights in the PBS data is due to the cohort being younger and therefore have a lower risk of death. As the c-statistic is calculated based on the predicted

probabilities and the count of concordant, discordant and tied pairs the c-statistic of 0.809 suggests the model is less effective in discriminating between those who did die and those who didn't.

Conclusion

The updated Rx-Risk index is a valid measure of comorbidity and strongly predicted one-year mortality in an outpatient population; irrespective of whether the index was modelled as a score or modelled as individual comorbidities. Modelling the Rx-Risk as individual covariates rather than an overall score (or count) was most predictive of one-year mortality and may be more useful in practice.

Contributor statement:
Research area and study design: NP MK ER EER Data acquisition: NP MK JB; data analysis and interpretation: NP MK ER AKC LK; statistical analysis: NP MK; Mapping of the ATC codes to the RxRisk categories; JB LK EER. All authors drafted, edited and approved the final manuscript.

Competing Interests:
None declared for any author.

Funding:
This work was funded by the Australian Government Department of Veterans' Affairs (DVA) as part of the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) program. EER is supported by NHMRC GNT 1110139. DVA reviewed this manuscript before submission but had no role in the design or conduct of this research.

Data sharing Agreement:
Data are available through the Australian Government Department of Veterans' Affairs

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Table 1: List of Rx-Risk comorbidity categories, corresponding Anatomical Therapeutic Chemical (ATC) codes, and score weightings in relation to 1-year mortality risk in DVA and PBS data.

Rx-Risk comorbidity category	ATC codes	DVA Data		PBS Data	
		N (%)	Weights for Rx-Risk score	N (%)	Weights for Rx-Risk score
Alcohol dependecy	N07BB01-N07BB99	183 (0.1)	6	137 (0.1)	0
Allergies	R01AC01-R01AD60, R06AD02-R06AX27, R06AB04	16684 (12)	-1	1095 (0.4)	2
Anticoagulants	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05	24863 (18)	1	35456 (12)	1
Antiplatelets	B01AC04-B01AC30	52525 (39)	2	50129 (17)	3
Anxiety	N05BA01-N05BA12, N05BE01	15615 (12)	1	24335 (8)	1
Arrhythmia	C01AA05, C01BA01-C01BD01, C07AA07	14992 (11)	2	19108 (6)	2
Benign prostatic hyperplasia	G04CA01-G04CA99, G04CB01, G04CB02[a]	9003 (7)	0	11933 (4)	-1
Bipolar disorder	N05AN01	231 (0.2)	-1	670 (0.2)	0
Chronic airways disease	R03AC02-R03DC03, R03DX05	33244 (25)	2	59873 (20)	2
Congestive heart failure	C03DA02-C03DA99, C07AB02 - if PBS[d] item code is 8732N, 8733P, 8734Q, 8735R, C07AB07, C07AG02, C07AB12, C03DA04, (C03CA01–C03CC01 AND C09AA01–C09AX99, C09CA01–C09CX99)[b]	23975 (8)	2	24851 (8)	4

Dementia	N06DA02-N06DA04, N06DX01	3868 (3)	2	4090 (1)	4
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX18, N06AX21-N06AX26	43354 (32)	2	63864 (21)	2
Diabetes	A10AA01-A10BX99	17550 (13)	2	48341 (16)	2
Epilepsy	N03AA01-N03AX99	15484 (11)	0	23520 (8)	2
Glaucoma	S01EA01-S01EB03, S01EC03-S01EX99	16262 (12)	0	22933 (8)	0
Gastroesophageal reflux disease	A02BA01-A02BX05	69358 (51)	0	124740 (41)	1
Gout	M04AA01-M04AC01	13723 (10)	1	21700 (7)	0
Hepatitis B	J05AF08, J05AF10, J05AF11	7 (0.01)	NA	80 (0.03)	NA
Hepatitis C	J05AB54, L03AB10, L03AB11, L03AB60, L03AB61, J05AE14, J05AE11-J05AE12, J05AX14, J05AX15, J05AX65, J05AB04	1 (0.0)	NA	12 (0.0)	NA
Human immunodeficiency virus	J05AE01-J05AE10, J05AF12-J05AG05, J05AR01-J05AR99, J05AX07-J05AX09, J05AX12, J05AF01-J05AF07, J05AF09	42 (0.03)	0	120 (0.04)	0
Hyperkalaemia	V03AE01	197 (0.2)	4	0 (0)	NA
Hyperlipidaemia	A10BH03[e], C10AA01-C10BX09	67690 (50)	-1	156214 (52)	-1
Hypertension	C03AA01-C03BA11, C03DB01, C03DB99, C03EA01, C09BA02-C09BA09, C09DA02-C09DA08, C02AB01-C02AC05, C02DB02-C02DB99, (C03CA01-C03CCO1 OR	71867 (53)	-1	162809 (54)	-1

	C09CA01-C09CX99)[c]				
Hyperthyroidism	H03BA02, H03BB01	992 (1)	2	1569 (1)	0
Hypothyroidism	H03AA01-H03AA02	13438 (10)	0	26630 (9)	1
Irritable bowel syndrome	A07EC01-A07EC04, A07EA01-A07EA02, A07EA06, L04AA33	1132 (1)	0	2586 (1)	-1
Ischaemic heart disease: angina	C01DA02-C01DA14, C01DX16, C08EX02	16988 (13)	2	19606 (7)	1
Ischaemic heart disease: hypertension	C07AA01-C07AA06, C07AA08-C07AB01, C07AB02 - if PBS[d] item code is not 8732N, 8733P, 8734Q, 8735R, C07AG01, C08CA01-C08DB01, C09DB01-C09DB04, C09DX01, C09BB02-C09BB10, C07AB03, C09DX03, C10BX03[f]	49947 (37)	-1	101575 (34)	-1
Incontinence	G04BD01-G04BD99	5554 (4)	0	6181 (2)	-1
Inflammation/pain	M01AB01-M01AH06	23510 (17)	-1	60996 (20)	-1
Liver failure	A06AD11, A07AA11	5034 (4)	3	4701 (2)	4
Malignancies	L01AA01-L01XX41	7689 (6)	2	7719 (3)	6
Malnutrition	B05BA01-B05BA10	16 (0.01)	0	19 (0.01)	0
Migraine	N02CA01-N02CX01	708 (1)	-1	2185 (1)	-1
Osteoporosis/Paget's	M05BA01-M05BB05, M05BX03, M05BX04, G03XC01, H05AA02	21448 (16)	-1	32338 (11)	0
Pain	N02AA01-N02AX02, N02AX06, N02AX52, N02BE51	44035 (33)	3	71755 (24)	4
Pancreatic insufficiency	A09AA02	433 (0.3)	0	930 (0.3)	6
Parkinsons	N04AA01-N04BX02	4237 (3)	3	6560 (2)	4

Psoriasis	D05AA01-D05AA99, D05BB01 D05BB02, D05AX02, D05AC01-D05AC51, D05AX52	1224 (1)	0	2487 (1)	0
Psychotic illness	N05AA01-N05AB02, N05AB06-N05AL07, N05AX07-N05AX13	7714 (6)	6	9390 (3)	6
Pulmonary hypertension	C02KX01-C02KX05, PBS[d] item code 9547L, 9605M	40 (0.03)	6	45 (0.01)	0
Renal disease	B03XA01-B03XA03, A11CC01-A11CC04, V03AE02, V03AE03, V03AE05	1816 (1)	6	2548 (1)	6
Smoking cessation	N07BA01-N07BA03, N06AX12	1145 (1)	6	2710 (1)	3
Steroid responsive disease	H02AB01-H02AB10	19106 (14)	2	35999 (12)	3
Transplant	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02	102 (0.1)	0	368 (0.1)	6
Tuberculosis	J04AC01-J04AC51, J04AM01-J04AM99	0	NA	17 (0.01)	NA

[a] Benign prostatic hyperplasia medicines are tested for gender - must be male. Females suffering from bladder obstructions can be prescribed medicines used to treat benign prostatic hyperplasia.
[b] Must have at least two medicines prescribed with one of those medicines having an Anatomical Therapeutic Chemical (ATC) code from C03CA01–C03CC01 and the other having an ATC code from either C09AA01–C09AX99 or C09CA01–C09CX99
[c] Can have medicine dispensed with an ATC code C03CA01–C03CC01 or C09AA01–C09AX99, but not both; as this would indicate chronic heart failure.
[d] Pharmaceutical Benefits Scheme
[e] Combination product for hyperlipidaemia and diabetes
[f] Combination product for hyperlipidaemia and ischaemic heart disease: hypertension

Table 2: Weighting algorithm used to score the Rx-Risk index.*

Odds ratio	P-value	Weighted Rx-Risk score
Any odds ratio	>0.10	0
<1	≤0.10	-1
1.0 ≤ and <1.2	≤0.10	1
1.2 ≤ and <1.4	≤0.10	2
1.4 ≤ and <1.6	≤0.10	3
1.6 ≤ and <1.8	≤0.10	4
1.8 ≤ and <2.0	≤0.10	5
≥2.0	≤0.10	6

*Weights are based on the size of odds ratio quantifying the probability of mortality in an outpatient population within one year, given treatment for a specified comorbidity.

Table 3: Comparison of different Rx-Risk scoring and modelling methods to predict one- year mortality in the DVA and PBS populations.

	DVA				PBS			
Models	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**
Base model (BM): age and sex	80538.5	-	0.738 (0.734, 0.742)	-	79527.9	-	0.761 (0.756, 0.766)	-
Rx-Risk measures								
BM + unweighted Rx-Risk	79420.1	1118.4	0.751 (0.747, 0.754)	14.0%, <.0001	77029.9	2498.0	0.796 (0.791, 0.800)	25.5%, <.0001
BM + DVA weighted Rx-Risk	76102.4	4436.1	0.786 (0.782, 0.789)	65.6%, <.0001	73143.8	6384.1	0.833 (0.829, 0.837)	92.0%, <.0001
BM + PBS weighted Rx-Risk	78573.5	1965.0	0.761 (0.757, 0.764)	26.4%, <.0001	75849.6	3678.3	0.809 (0.805, 0.813)	44.0%, <.0001
BM + 43 comorbidity indicators	75692.2	4846.3	0.791 (0.788, 0.795)	73.9%, <.0001	71689.1	7838.8	0.845 (0.842, 0.849)	114.8%, <.0001
Crude measures								
BM + prescription count	79105.9	1432.6	0.755 (0.751, 0.759)	18.6%, <.0001	76762.8	2765.1	0.799 (0.795, 0.804)	31.4%, <.0001
BM + unique ATC[d] medicine count	78374.5	2164.0	0.762 (0.758, 0.766)	29.4%, <.0001	75369.1	4158.8	0.814 (0.810, 0.818)	50.0%, <.0001
BM + unique PBS[e] medicine count	78210.2	2328.3	0.764 (0.760, 0.768)	32.1%, <.0001	75108.8	4419.1	0.816 (0.812, 0.820)	55.8%, <.0001

[a] AIC: Akaike information criterion model. The model with the lowest AIC value is considered the best fit.

[b] AIC score compared to the AIC score of the base model. A model with a lower score of 10 (or more) is considered superior.

[c] Possible range 0-1, with 1 indicating perfect prediction and 0.5 indicating chance prediction. A c-statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable.

[d] Anatomical Chemical Therapeutic classification system, count based on the number of unique ATC codes dispensed.
[e] Pharmaceutical Benefits Scheme, count based on the number of unique PBS item codes dispensed.

BMJ Open

The validity of the Rx-Risk comorbidity index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) classification system

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021122.R1
Article Type:	Research
Date Submitted by the Author:	11-Feb-2018
Complete List of Authors:	Pratt, Nicole; University of South Australia, Sansom Institute for Health Research Kerr, Mhairi ; University of South Australia, Sansom Institute for Health Research Barratt, John; University of South Australia, Sansom Institute for Health Research Kemp-Casey, Anna; University of South Australia, Sansom Institute for Health Research Kalisch Ellett, Lisa; University of South Australia, Sansom Institute for Health Research Ramsay, Emmae; University of South Australia, Sansom Institute for Health Research Roughead, Elizabeth; University of South Australia, Sansom Institute for Health Research
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	chronic disease burden, comorbidity, mortality prediction, model validation, claims data, weighting

Title: The validity of the Rx-Risk comorbidity index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) classification system

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Key words: chronic disease burden, claims data, comorbidity, weighting, mortality prediction, model validation.

Word Count: 2819

Ethics Statement
This research was approved by the Australian Government Department of Veterans' Affairs (DVA) Human Research Ethics Committee and the University of South Australia Human Research Ethics Committee

Abstract (300 words allowed)

Objectives: To provide a map of Anatomical Therapeutic Chemical (ATC) classification system codes to individual Rx-Risk comorbidities and to validate the Rx-Risk comorbidity index.

Design: The 46 comorbidities in the Rx-Risk index were mapped to dispensing's indicative of each condition using ATC codes. Prescription dispensing claims in 2014 were used to calculate the Rx-Risk. A baseline logistic regression model was fitted using age and gender as covariates. Rx-risk was added to the base model as an (i) unweighted score, (ii) weighted score, and as (iii) individual comorbidity categories indicating the presence or absence of each condition. The Akaike information criterion (AIC) and c-statistic were used to compare the models.

Setting: Models were developed in the Australian Government Department of Veterans' Affairs health claims data and external validation was undertaken in a 10% sample of the Australian Pharmaceutical Benefits Scheme Data.

Participants: Subjects aged 65 years or older

Outcome measures: Death within one year (eg 2015)

Results: Compared to the base model (c-statistic 0.738, 95% Confidence Interval (CI) 0.734-0.742), including Rx-Risk improved prediction of mortality; unweighted score 0.751, 95%CI 0.747-0.754, weighted score 0.786, 95%CI 0.782-0.789 and individual comorbidities 0.791, 95%CI 0.788-0.795. External validation confirmed the utility of the weighted index (c-statistic=0.833).

Conclusions: The updated Rx-Risk comorbidity score was predictive of one-year mortality and may be useful in practice to adjust for confounding in observational studies using medication claims data.

Strength and Limitations of this study (5 bullet points that relate to methods. No results)

Strengths

- This study provides an up to date list of medicines identified by ATC codes mapped to individual Rx-Risk categories
- Rx-Risk mapped to ATC codes can be easily adapted for use in other health systems making this index a useful resource for researchers worldwide

Limitations

- The Rx-Risk index has been updated and mapped to ATC codes based on medicine availability in Australia; hence modifications may be required for use in other health systems
- This study was limited to patients over 65 years of age so Rx-Risk category weights derived in this study may not be applicable to younger populations.

Introduction

The prevalence of multimorbidity in the population is increasing [1, 2] and patients with multiple conditions are at greater risk of adverse outcomes [3]. In observational studies, in which the aim is to determine the association between medicine use and adverse events, adjustment for multimorbidity is required to avoid biased results. Reliable methods for identifying and controlling for multiple comorbidities are required in order to make valid comparisons between treatments. The Rx-Risk is a measure for determining an individual's current comorbidities based on their prescription medicine dispensing [4, 5]. It was initially developed for predicting costs of health care [6] and was subsequently adapted to predict mortality in outpatient populations [7, 8]. Rx-Risk has been found to be a better predictor of one- and three-year mortality (one-year mortality: weighted Rx-Risk c-statistic=0.728, 95% CI=0.723-0.733, three-year mortality: 0.731, 95%CI=0.728-0.734) compared to simple prescription counts in the same time periods (one-year mortality: 0.715, 95%CI=0.710-0.720, three-year mortality: 0.718, 95%CI=0.715- 0.721) [9].

The first pharmacy based measure of comorbidity, developed in 1992, was The Chronic Disease Score (CDS) [4], consisting of 17 comorbidity categories. The CDS was subsequently updated and renamed in 2003 as the Rx-Risk-V index, consisting of 45 categories of comorbidity [10]. The Rx-Risk-V index was then adapted to only include comorbidities for which a medicine could be prescribed and therefore could be applied to prescription claims data resulting in an index based on 42 categories of comorbidity [11]. Due to continual advances in pharmaceutical disease management and as new medicines are used to treat particular diseases, e.g. treatment for hepatitis B and C, the Rx-Risk requires periodical

updating and re-validation. A list of Rx-Risk comorbidities and their corresponding medicines mapped to a standardised international coding system has not been published previously and would facilitate use of the index across health systems. Other comorbidity scores such as the Elixhauser and Charlson Index [12, 13] require diagnostic information in their construction. The advantage of the RxRisk is that it requires prescription data only and provides researchers with the ability to measure comorbidity even in a predominately outpatient setting.

The aim of this study was to facilitate the use of the RxRisk in practice by providing a list of the individual RxRisk categories mapped, using clinical expertise, to the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system [14] and to determine the validity of the Rx-Risk index, in predicting one-year mortality in an outpatient population.

Method

Rx-Risk index mapping

The Rx-Risk index consists of 46 comorbidity categories. For each Rx-Risk category, medicines indicative of that condition were mapped (see Table 1). This mapping was performed at the ATC classification level and performed by consensus between two pharmacists. If an individual had ≥1 dispensing for a medicine in a given category then they were considered to have been treated (using medicines) for that comorbidity. Medications in both the DVA and PBS datasets are coded using the World Health Organisation anatomical therapeutic chemical (ATC) classification system [14] and PBS item codes [15].

Data sources

The primary data source was the Australian Government Department of Veterans' Affairs (DVA's) administrative claims database. This database contains details of all prescription medicines, medical and allied health services, and hospitalisations subsidised by DVA. The current treatment population consists of 223,181 members of the Australian veteran community, which includes veterans, war widows and widowers. The median age of the DVA treatment population is 75 years and 62% are men. DVA also maintains a client file containing gender, date of birth and date of death information.

External validation of the Rx-Risk index was conducted using the Pharmaceutical Benefits Scheme (PBS) 10% sample of the Australian population. This dataset contains information on the dispensing of prescription medicines, and includes basic demographic information regarding gender, year of birth and year of death. It is maintained by the Australian Government Department of Human Services. The current treatment population consists of 1,346,340 members of the Australian community. The median age of the PBS treatment population is 43 years and 48% are men.

Study population

The DVA study population included individuals with at least one health care encounter in the six month period from 1 July 2013 to 31 December 2013. A health care encounter included any of the following: a medication dispensing, a doctor's visit, or hospitalisation. Analysis was restricted to veterans who were DVA Gold Card holders prior to 1 July 2013 (ensuring they were eligible for all DVA subsidised services, thus the data set captured all their health claims), and were between the ages of 65 and 100 years at 1 January 2015 (N=135,406). Inclusion criteria for the PBS cohort were people with a health care encounter

(defined as at least one medicine dispensing) in the six month period from 1 July 2013 to 31 December 2013, who were aged between 65 and 100 years at 1 January 2015 (N=303,135). The primary outcome for this study was death recorded in 2015, hence patients were only included if they were alive as at 1 January 2015. Rx-Risk scores were calculated separately in each dataset using prescription claims for supplied medicines over a one-year baseline period between 1 January 2014 and 31 December 2014.

Calculating Rx-Risk scores and prescription counts

The full Rx-Risk index has 46 comorbidity categories; however, tuberculosis, and hepatitis B and C were removed from the Rx-Risk index for this study as the number of individuals with these conditions in the DVA cohort was less than 10 so weights could not be generated. This resulted in 43 categories in the validation study. The following forms of the Rx-Risk score were generated. The unweighted Rx-Risk score was calculated as the count of the number of different comorbidity categories for which an individual was treated with a possible score ranging from 0 to 43. The weighted Rx-Risk score was calculated by adding the 43 indicator variables to a logistic regression model with mortality as the outcome including age and gender as covariates. From this model each comorbidity category was assigned a weight according to the statistical significance and magnitude of the odds ratio generated from the logistic regression model (Table 2)[7]. The weighted Rx-Risk score for an individual was then the sum of the weighted indicator variables. As an example, the unweighted RxRisk score for a patient who has two comorbidities 'Pain' and 'Renal disease' is 2, while their weighted Rx Score is 9 that is the sum of the weight for 'Pain' (3) and 'Renal Disease' (6).

[Insert Table 2 here]

Three crude prescription counts were also calculated: (i) total number of prescriptions dispensed in the baseline period (1 January 2014 – 31 December 2014), (ii) total number of unique medicines dispensed in the baseline period based on ATC codes, and (iii) total number of unique medicines dispensed during the baseline period based on PBS item codes[15]. The distinction between ATC and PBS codes was made because different strengths or formulations of the same medicine have the same ATC code but different PBS codes; e.g. if a patient is dispensed two different strengths of the same medicine, this will be counted once in the total number of ATC medicines dispensed but twice in the total number of PBS medicines dispensed.

Statistical analysis

Primary analysis was performed in the DVA database. A baseline logistic regression model was calculated for mortality using age and gender as predictors. The comorbidity scores, individual comorbidities, and crude prescription counts were added to the baseline model separately. Age, comorbidity scores and crude prescription measures were included in the models as continuous variables assuming linear associations. Models using the individual comorbidities were developed with an indicator variable included for the presence (1) or absence (0) of each individual RxRisk category. The overall goodness-of-fit of each model was compared to the baseline model using the Akaike Information criterion (AIC)[16]. The model with the lowest AIC value is considered the best fit. The difference between the AIC values of two models must be greater than 10 for one model to be considered superior to the other. Model discrimination was compared based on the c-statistic and the relative Integrated Discrimination Improvement (IDI) [17]. The value of the c-statistic can range from 0 to 1, with 1 indicating perfect prediction and 0.5 indicating chance predictions. A c-

statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable[18]. Using 1000 bootstrap samples 95% confidence intervals were calculated for the c-statistics[9].

Internal validation of weighted scores

We used 10-fold cross-validation to internally validate the binary logistic regression model used to calculate the Rx-Risk category weights. This subsets the DVA cohort, using random sampling without replacement, into 10 equal folds. Each fold is a 10% subset of the DVA cohort. The training set consisted of 9 folds and was used to calculate Rx-Risk category weights. The calculated weights were then applied to the testing set (i.e. fold left out of training set). A binary logistic regression model of one- year mortality including age, gender and weighted Rx-Risk was built separately for the training set and testing set and the c-statistics recorded. This process was repeated ten times until each fold was used as the testing set once. This resulted in 20 c-statistics being calculated, 10 each on the training and testing set. The average c-statistic was recorded for each set.

Sensitivity analyses

Two sensitivity analyses were carried out. In the first sensitivity analysis we used the lower confidence limit of the odds ratio to determine the Rx-Risk category weights rather than the estimated odds ratio itself. We did this as some comorbidities are uncommon in this population resulting in large confidence intervals. In the second sensitivity analysis we calculated the Rx-Risk category weights (based on the odds ratio) generated from 5000 bootstrap samples. For each Rx-Risk category the weight was calculated as the median of

the 5000 weights for that category generated in each bootstrap sample. We did this sensitivity analysis to test the stability of the weights.

External Validation

To determine the external validity of the weights, the calculated Rx-Risk category weights derived from the DVA dataset were applied to the PBS cohort. The Akaike information criterion model fit and c-statistics were calculated to determine the validity of the model.

Results

Table 1 presents the ATC mapped Rx-Risk categories, derived empirical weights, and number of treated individuals in the DVA populations. The most frequent comorbidities identified by the Rx-Risk index in the DVA cohort were hypertension (53%), gastro-oesophageal reflux disease (GORD) (51%), hyperlipidaemia (50%), and conditions treated with antiplatelets (39%). In the DVA cohort of 135,406 people, with a mean age of 83 years (standard deviation (SD) 9.5) and 47% were men. The median unweighted Rx-Risk score was 5 (interquartile range (IQR) 3-7) and the median weighted Rx-Risk score was 3 (0-6).

The baseline model, comprising only age and gender, predicted one-year mortality moderately well in the DVA cohort (c-statistic=0.738, 95% Confidence Interval (CI) 0.734-0.742). The addition of Rx-Risk to the model increased the performance of the model: unweighted Rx-Risk c-statistic=0.751, (95% CI 0.747-0.754), IDI=14.0%, p-value<.0001; weighted Rx-Risk c-statistic=0.786, (95% CI=0.782-0.789), IDI=65.6%, p-value<.0001; 43 individual comorbidities c-statistic=0.791, (95% CI=0.788-0.795), IDI=73.9%, p-value<.0001. The model including the 43 comorbidity indicator variables had the lowest AIC (75692),

highest c-statistic (0.791), and the highest discrimination improvement (73.9%). The models including the weighted Rx-Risk score or 43 comorbidity measures were better predictors of one-year mortality than any of the crude prescription measures (Table 3). Results of the internal 10-fold cross validation were consistent with the main analysis with an average c-statistic of 0.785 achieved over the 10 testing datasets compared to a c-statistic of 0.786 in the primary analysis.

[Insert Table 3 here]

In the sensitivity analysis using the lower 95% confidence interval limit in the weighting algorithm we found a very similar performance with a c-statistic of 0.787 compared to the weighting algorithm using the estimated odds ratio (c-statistic 0.786). In the second sensitivity analysis in which the weights were calculated from 5000 bootstrap samples we found a similar c-statistic (0.786) compared to the primary analysis.

The PBS cohort consisted of 303,135 people, with an mean age of 75 years (standard deviation (SD) 7.4) and 45% were men. Similar to the DVA cohort, the most frequent comorbidities identified by the Rx-Risk index in the PBS cohort were hypertension (54%), hyperlipidaemia (52%) and gastro-oesophageal reflux disease (GORD) (41%). When the DVA derived Rx-risk category weights were applied to the PBS population we found a c-statistic of 0.833 (Table 3) showing good external validity.

Discussion

This paper presents the Rx-Risk index with each comorbidity category mapped to medicines at the ATC classification level using clinical expertise. The mapped index provides a resource

for researchers working with health claims data utilising ATC codes or that have mappings to the ATC codes to calculate comorbidity, based on prescription medicine dispensing's in an outpatient population. We have shown that the updated Rx-Risk was highly predictive of one-year mortality in both the populations examined and is a valid measure of comorbidity in an outpatient population and is therefore likely to be useful in a range of observational data settings.

All forms of Rx-Risk predicted mortality better than just age and sex alone. The best results for predicting one-year mortality were achieved when modelling Rx-Risk as individual comorbidities or as a weighted score. The unweighted Rx-Risk score had similar performance to simple prescription medicine counts. Internal and external validation showed that the weighted index was predictive of one-year mortality within the veteran population and show good external validity when applied to a general population setting. These results suggest that the weighted RxRisk score is likely to be generalizable to other populations. Making the ATC map available to researchers will facilitate the use of the Rx-Risk in place of comorbidity estimated simply by prescription counts.

The Rx-Risk index has been updated accounting for the introduction of new medicines to the market, making this index a useful resource for researchers. The updated Rx-Risk has 46 comorbidities, however 3 (tuberculosis, and hepatitis B and C) were removed in the analysis stage as there were insufficient cases in the DVA cohort. A younger or larger sample may have allowed these comorbidities to be assessed. For consistency, these comorbidities were also excluded from the analysis in the PBS cohort despite there being few but sufficient cases. The Rx-Risk index has been updated and mapped to ATC codes based on medicine

availability in Australia; hence modifications may be required for use in other health systems.

The health care encounter inclusion criteria were not the same for both cohorts. The DVA cohort included people with a hospitalisation or GP visit, while the PBS cohort was limited to those with a prescription dispensing only. However, the difference across populations is small, as 96.7% of the DVA cohort had a medication dispensed in the six month selection period.

Comorbidity scores are often used in observational studies to reduce the potential for confounding. The advantage of these summary scores is that they simplify the inclusion of individual covariates for each comorbidity into a single summary score. This is a particular advantage when sample sizes are small or the outcome under study is rare. Our analysis demonstrated that the performance of the weighted RxRisk score performed as well as the model which included each individual comorbidity category. Additionally, including all individual comorbidities as indicator variables may not be appropriate in some studies, such as those looking at the effect of a particular treatment on an adverse event when the treatment itself is included in the construction of the comorbidity score. For example, when determining whether the risk of NSAIDS is associated with gastrointestinal bleeds, it would not be correct to adjust for inflammation/pain as an indicator as the medicines mapped to this comorbidity include NSAIDs. In this scenario it would be advisable to remove inflammation/pain as an indicator or use the weighted Rx-Risk score. Lastly, although the weighted RxRisk score performed well in the PBS data set, which suggests that the weights have a good external validity, the Rx-Risk category weights derived in this study may not be applicable to all external populations. We limited our cohorts to patients over 65 years of

age so factors that are predictors of mortality in this age group may not be predictors in a younger group.

Conclusion

The updated Rx-Risk comorbidity score is a valid measure of comorbidity and strongly predicted one-year mortality in an outpatient population. The weighted Rx-Risk score was found to be valid in an external population and may be useful in practice to adjust for confounding in observational studies using medication claims data.

Contributor statement:
Research area and study design: NP MK ER EER Data acquisition: NP MK JB; data analysis and interpretation: NP MK ER AKC LK; statistical analysis: NP MK; Mapping of the ATC codes to the RxRisk categories; JB LK EER. All authors drafted, edited and approved the final manuscript.

Competing Interests:
None declared for any author.

Funding:
This work was funded by the Australian Government Department of Veterans' Affairs (DVA) as part of the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) program. EER is supported by NHMRC GNT 1110139. DVA reviewed this manuscript before submission but had no role in the design or conduct of this research.

Data sharing Agreement:
Data are available through the Australian Government Department of Veterans' Affairs

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Table 1: List of Rx-Risk comorbidity categories, corresponding Anatomical Therapeutic Chemical (ATC) codes, and score weightings in relation to 1-year mortality risk in DVA and PBS data.

Rx-Risk comorbidity category	ATC codes	DVA Data	
		N (%)	Weights for Rx-Risk score
Alcohol dependecy	N07BB01-N07BB99	183 (0.1)	6
Allergies	R01AC01-R01AD60, R06AD02-R06AX27, R06AB04	16684 (12)	-1
Anticoagulants	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05	24863 (18)	1
Antiplatelets	B01AC04-B01AC30	52525 (39)	2
Anxiety	N05BA01-N05BA12, N05BE01	15615 (12)	1
Arrhythmia	C01AA05, C01BA01-C01BD01, C07AA07	14992 (11)	2
Benign prostatic hyperplasia	G04CA01-G04CA99, G04CB01, G04CB02[a]	9003 (7)	0
Bipolar disorder	N05AN01	231 (0.2)	-1
Chronic airways disease	R03AC02-R03DC03, R03DX05	33244 (25)	2
Congestive heart failure	C03DA02-C03DA99, C07AB02 - if PBS[d] item code is 8732N, 8733P, 8734Q, 8735R, C07AB07, C07AG02, C07AB12, C03DA04, (C03CA01–C03CC01 AND C09AA01–C09AX99, C09CA01–C09CX99)[b]	23975 (8)	2

Dementia	N06DA02-N06DA04, N06DX01	3868 (3)	2
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX18, N06AX21-N06AX26	43354 (32)	2
Diabetes	A10AA01-A10BX99	17550 (13)	2
Epilepsy	N03AA01-N03AX99	15484 (11)	0
Glaucoma	S01EA01-S01EB03, S01EC03-S01EX99	16262 (12)	0
Gastroesophageal reflux disease	A02BA01-A02BX05	69358 (51)	0
Gout	M04AA01-M04AC01	13723 (10)	1
Hepatitis B	J05AF08, J05AF10, J05AF11	7 (0.01)	NA
Hepatitis C	J05AB54, L03AB10, L03AB11, L03AB60, L03AB61, J05AE14, J05AE11-J05AE12, J05AX14, J05AX15, J05AX65, J05AB04	1 (0.0)	NA
Human immunodeficiency virus	J05AE01-J05AE10, J05AF12-J05AG05, J05AR01-J05AR99, J05AX07-J05AX09, J05AX12, J05AF01-J05AF07, J05AF09	42 (0.03)	0
Hyperkalaemia	V03AE01	197 (0.2)	4
Hyperlipidaemia	A10BH03[e], C10AA01-C10BX09	67690 (50)	-1
Hypertension	C03AA01-C03BA11, C03DB01, C03DB99, C03EA01, C09BA02-C09BA09, C09DA02-C09DA08, C02AB01-C02AC05, C02DB02-C02DB99, (C03CA01-C03CCO1 OR C09CA01-C09CX99)[c]	71867 (53)	-1

Hyperthyroidism	H03BA02, H03BB01	992 (1)	2
Hypothyroidism	H03AA01-H03AA02	13438 (10)	0
Irritable bowel syndrome	A07EC01-A07EC04, A07EA01-A07EA02, A07EA06, L04AA33	1132 (1)	0
Ischaemic heart disease: angina	C01DA02-C01DA14, C01DX16, C08EX02	16988 (13)	2
Ischaemic heart disease: hypertension	C07AA01-C07AA06, C07AA08-C07AB01, C07AB02 - if PBS[d] item code is not 8732N, 8733P, 8734Q, 8735R, C07AG01, C08CA01-C08DB01, C09DB01-C09DB04, C09DX01, C09BB02-C09BB10, C07AB03, C09DX03, C10BX03[f]	49947 (37)	-1
Incontinence	G04BD01-G04BD99	5554 (4)	0
Inflammation/pain	M01AB01-M01AH06	23510 (17)	-1
Liver failure	A06AD11, A07AA11	5034 (4)	3
Malignancies	L01AA01-L01XX41	7689 (6)	2
Malnutrition	B05BA01-B05BA10	16 (0.01)	0
Migraine	N02CA01-N02CX01	708 (1)	-1
Osteoporosis/Paget's	M05BA01-M05BB05, M05BX03, M05BX04, G03XC01, H05AA02	21448 (16)	-1
Pain	N02AA01-N02AX02, N02AX06, N02AX52, N02BE51	44035 (33)	3
Pancreatic insufficiency	A09AA02	433 (0.3)	0
Parkinsons	N04AA01-N04BX02	4237 (3)	3
Psoriasis	D05AA01-D05AA99,	1224 (1)	0

	D05BB01 D05BB02, D05AX02, D05AC01-D05AC51, D05AX52		
Psychotic illness	N05AA01-N05AB02, N05AB06-N05AL07, N05AX07-N05AX13	7714 (6)	6
Pulmonary hypertension	C02KX01-C02KX05, PBS[d] item code 9547L, 9605M	40 (0.03)	6
Renal disease	B03XA01-B03XA03, A11CC01-A11CC04, V03AE02, V03AE03, V03AE05	1816 (1)	6
Smoking cessation	N07BA01-N07BA03, N06AX12	1145 (1)	6
Steroid responsive disease	H02AB01-H02AB10	19106 (14)	2
Transplant	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02	102 (0.1)	0
Tuberculosis	J04AC01-J04AC51, J04AM01-J04AM99	0	NA

[a] Benign prostatic hyperplasia medicines are tested for gender - must be male. Females suffering from bladder obstructions can be prescribed medicines used to treat benign prostatic hyperplasia.
[b] Must have at least two medicines prescribed with one of those medicines having an Anatomical Therapeutic Chemical (ATC) code from C03CA01–C03CC01 and the other having an ATC code from either C09AA01–C09AX99 or C09CA01–C09CX99
[c] Can have medicine dispensed with an ATC code C03CA01–C03CC01 or C09AA01–C09AX99, but not both; as this would indicate chronic heart failure.
[d] Pharmaceutical Benefits Scheme
[e] Combination product for hyperlipidaemia and diabetes
[f] Combination product for hyperlipidaemia and ischaemic heart disease: hypertension

Table 2: Weighting algorithm used to score the Rx-Risk index.*

Odds ratio	P-value	Weighted Rx-Risk score
Any odds ratio	>0.10	0
<1	≤0.10	-1
1.0 ≤ and <1.2	≤0.10	1
1.2 ≤ and <1.4	≤0.10	2
1.4 ≤ and <1.6	≤0.10	3
1.6 ≤ and <1.8	≤0.10	4
1.8 ≤ and <2.0	≤0.10	5
≥2.0	≤0.10	6

*Weights are based on the size of odds ratio quantifying the probability of mortality in an outpatient population within one year, given treatment for a specified comorbidity.

Table 3: Comparison of different Rx-Risk scoring and modelling methods to predict one- year mortality in the DVA population and external validation using the PBS population.

	DVA				PBS			
Models	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**
Base model (BM): age and sex	80538.5	-	0.738 (0.734, 0.742)	-	79527.9	-	0.761 (0.756, 0.766)	-
Rx-Risk measures								
BM + unweighted Rx-Risk	79420.1	1118.4	0.751 (0.747, 0.754)	14.0%, <.0001	77029.9	2498.0	0.796 (0.791, 0.800)	25.5%, <.0001
BM + DVA weighted Rx-Risk	76102.4	4436.1	0.786 (0.782, 0.789)	65.6%, <.0001	73143.8	6384.1	0.833 (0.829, 0.837)	92.0%, <.0001
BM + 43 comorbidity indicators	75692.2	4846.3	0.791 (0.788, 0.795)	73.9%, <.0001	71689.1	7838.8	0.845 (0.842, 0.849)	114.8%, <.0001
Crude measures								
BM + prescription count	79105.9	1432.6	0.755 (0.751, 0.759)	18.6%, <.0001	76762.8	2765.1	0.799 (0.795, 0.804)	31.4%, <.0001
BM + unique ATC[d] medicine count	78374.5	2164.0	0.762 (0.758, 0.766)	29.4%, <.0001	75369.1	4158.8	0.814 (0.810, 0.818)	50.0%, <.0001
BM + unique PBS Item Code[e] medicine count	78210.2	2328.3	0.764 (0.760, 0.768)	32.1%, <.0001	75108.8	4419.1	0.816 (0.812, 0.820)	55.8%, <.0001

[a] AIC: Akaike information criterion model. The model with the lowest AIC value is considered the best fit.
[b] AIC score compared to the AIC score of the base model. A model with a lower score of 10 (or more) is considered superior.

[c] Possible range 0-1, with 1 indicating perfect prediction and 0.5 indicating chance prediction. A c-statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable.
[d] Anatomical Chemical Therapeutic classification system, count based on the number of unique ATC codes dispensed.
[e] Pharmaceutical Benefits Scheme, count based on the number of unique PBS item codes dispensed.

BMJ Open

The validity of the Rx-Risk comorbidity index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) classification system

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021122.R2
Article Type:	Research
Date Submitted by the Author:	15-Mar-2018
Complete List of Authors:	Pratt, Nicole; University of South Australia, Sansom Institute for Health Research Kerr, Mhairi ; University of South Australia, Sansom Institute for Health Research Barratt, John; University of South Australia, Sansom Institute for Health Research Kemp-Casey, Anna; University of South Australia, Sansom Institute for Health Research Kalisch Ellett, Lisa; University of South Australia, Sansom Institute for Health Research Ramsay, Emmae; University of South Australia, Sansom Institute for Health Research Roughead, Elizabeth; University of South Australia, Sansom Institute for Health Research
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	chronic disease burden, comorbidity, mortality prediction, model validation, claims data, weighting

Title: The validity of the Rx-Risk comorbidity index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) classification system

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Key words: chronic disease burden, claims data, comorbidity, weighting, mortality prediction, model validation.

Word Count: 2819

Ethics Statement
This research was approved by the Australian Government Department of Veterans' Affairs (DVA) Human Research Ethics Committee and the University of South Australia Human Research Ethics Committee

Abstract (300 words allowed)

Objectives: To provide a map of Anatomical Therapeutic Chemical (ATC) classification system codes to individual Rx-Risk comorbidities and to validate the Rx-Risk comorbidity index.

Design: The 46 comorbidities in the Rx-Risk index were mapped to dispensing's indicative of each condition using ATC codes. Prescription dispensing claims in 2014 were used to calculate the Rx-Risk. A baseline logistic regression model was fitted using age and gender as covariates. Rx-risk was added to the base model as an (i) unweighted score, (ii) weighted score, and as (iii) individual comorbidity categories indicating the presence or absence of each condition. The Akaike information criterion (AIC) and c-statistic were used to compare the models.

Setting: Models were developed in the Australian Government Department of Veterans' Affairs health claims data and external validation was undertaken in a 10% sample of the Australian Pharmaceutical Benefits Scheme Data.

Participants: Subjects aged 65 years or older

Outcome measures: Death within one year (eg 2015)

Results: Compared to the base model (c-statistic 0.738, 95% Confidence Interval (CI) 0.734-0.742), including Rx-Risk improved prediction of mortality; unweighted score 0.751, 95%CI 0.747-0.754, weighted score 0.786, 95%CI 0.782-0.789 and individual comorbidities 0.791, 95%CI 0.788-0.795. External validation confirmed the utility of the weighted index (c-statistic=0.833).

Conclusions: The updated Rx-Risk comorbidity score was predictive of one-year mortality and may be useful in practice to adjust for confounding in observational studies using medication claims data.

Strength and Limitations of this study (5 bullet points that relate to methods. No results)

Strengths

- This study provides an up to date list of medicines identified by ATC codes mapped to individual Rx-Risk categories
- Rx-Risk mapped to ATC codes can be easily adapted for use in other health systems making this index a useful resource for researchers worldwide

Limitations

- The Rx-Risk index has been updated and mapped to ATC codes based on medicine availability in Australia; hence modifications may be required for use in other health systems
- This study was limited to patients over 65 years of age so Rx-Risk category weights derived in this study may not be applicable to younger populations.

Introduction

The prevalence of multimorbidity in the population is increasing [1, 2] and patients with multiple conditions are at greater risk of adverse outcomes [3]. In observational studies, in which the aim is to determine the association between medicine use and adverse events, adjustment for multimorbidity is required to avoid biased results. Reliable methods for identifying and controlling for multiple comorbidities are required in order to make valid comparisons between treatments. The Rx-Risk is a measure for determining an individual's current comorbidities based on their prescription medicine dispensing [4, 5]. It was initially developed for predicting costs of health care [6] and was subsequently adapted to predict mortality in outpatient populations [7, 8]. Rx-Risk has been found to be a better predictor of one- and three-year mortality (one-year mortality: weighted Rx-Risk c-statistic=0.728, 95% CI=0.723-0.733, three-year mortality: 0.731, 95%CI=0.728-0.734) compared to simple prescription counts in the same time periods (one-year mortality: 0.715, 95%CI=0.710-0.720, three-year mortality: 0.718, 95%CI=0.715- 0.721) [9].

The first pharmacy based measure of comorbidity, developed in 1992, was The Chronic Disease Score (CDS) [4], consisting of 17 comorbidity categories. The CDS was subsequently updated and renamed in 2003 as the Rx-Risk-V index, consisting of 45 categories of comorbidity [10]. The Rx-Risk-V index was then adapted to only include comorbidities for which a medicine could be prescribed and therefore could be applied to prescription claims data resulting in an index based on 42 categories of comorbidity [11]. Due to continual advances in pharmaceutical disease management and as new medicines are used to treat particular diseases, e.g. treatment for hepatitis B and C, the Rx-Risk requires periodical updating and re-validation. Additionally, the original published weights for the RxRisk score

were calculated by predicting cost of treatment rather than risk of death which is a more clinically relevant outcome [6]. A list of Rx-Risk comorbidities and their corresponding medicines mapped to a standardised international coding system has not been published previously and would facilitate use of the index across health systems. Other comorbidity scores such as the Elixhauser and Charlson Index [12, 13] require diagnostic information in their construction. The advantage of the RxRisk is that it requires prescription data only and provides researchers with the ability to measure comorbidity even in a predominately outpatient setting.

The aim of this study was to facilitate the use of the RxRisk in practice by providing a list of the individual RxRisk categories mapped, using clinical expertise, to the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system [14] and to determine the validity of the Rx-Risk index, in predicting one-year mortality in an outpatient population.

Method

Rx-Risk index mapping

The Rx-Risk index consists of 46 comorbidity categories. For each Rx-Risk category, medicines indicative of that condition were mapped (see Table 1). This mapping was performed at the ATC classification level and performed by consensus between two pharmacists. If an individual had ≥1 dispensing for a medicine in a given category then they were considered to have been treated (using medicines) for that comorbidity. Medications

in both the DVA and PBS datasets are coded using the World Health Organisation anatomical therapeutic chemical (ATC) classification system [14] and PBS item codes [15].

Data sources

The primary data source was the Australian Government Department of Veterans' Affairs (DVA's) administrative claims database. This database contains details of all prescription medicines, medical and allied health services, and hospitalisations subsidised by DVA. The current treatment population consists of 223,181 members of the Australian veteran community, which includes veterans, war widows and widowers. The median age of the DVA treatment population is 75 years and 62% are men. DVA also maintains a client file containing gender, date of birth and date of death information.

External validation of the Rx-Risk index was conducted using the Pharmaceutical Benefits Scheme (PBS) 10% sample of the Australian population. This dataset contains information on the dispensing of prescription medicines, and includes basic demographic information regarding gender, year of birth and year of death. It is maintained by the Australian Government Department of Human Services. The current treatment population consists of 1,346,340 members of the Australian community. The median age of the PBS treatment population is 43 years and 48% are men.

Patient and Public Involvement

Patients and public were not involved in this research. .

Study population

The DVA study population included individuals with at least one health care encounter in the six month period from 1 July 2013 to 31 December 2013. A health care encounter

included any of the following: a medication dispensing, a doctor's visit, or hospitalisation. Analysis was restricted to veterans who were DVA Gold Card holders prior to 1 July 2013 (ensuring they were eligible for all DVA subsidised services, thus the data set captured all their health claims), and were between the ages of 65 and 100 years at 1 January 2015 (N=135,406). Inclusion criteria for the PBS cohort were people with a health care encounter (defined as at least one medicine dispensing) in the six month period from 1 July 2013 to 31 December 2013, who were aged between 65 and 100 years at 1 January 2015 (N=303,135). The primary outcome for this study was death recorded in 2015, hence patients were only included if they were alive as at 1 January 2015. Rx-Risk scores were calculated separately in each dataset using prescription claims for supplied medicines over a one-year baseline period between 1 January 2014 and 31 December 2014.

Calculating Rx-Risk scores and prescription counts

The full Rx-Risk index has 46 comorbidity categories; however, tuberculosis, and hepatitis B and C were removed from the Rx-Risk index for this study as the number of individuals with these conditions in the DVA cohort was less than 10 so weights could not be generated. This resulted in 43 categories in the validation study. The following forms of the Rx-Risk score were generated. The unweighted Rx-Risk score was calculated as the count of the number of different comorbidity categories for which an individual was treated with a possible score ranging from 0 to 43. The weighted Rx-Risk score was calculated by adding the 43 indicator variables to a logistic regression model with mortality as the outcome including age and gender as covariates. From this model each comorbidity category was assigned a weight according to the statistical significance and magnitude of the odds ratio generated from the logistic regression model (Table 2)[7]. The weighted Rx-Risk score for an individual was then the sum of the weighted indicator variables. As an example, the unweighted RxRisk score for a

patient who has two comorbidities 'Pain' and 'Renal disease' is 2, while their weighted Rx Score is 9 that is the sum of the weight for 'Pain' (3) and 'Renal Disease' (6).

[Insert Table 2 here]

Three crude prescription counts were also calculated: (i) total number of prescriptions dispensed in the baseline period (1 January 2014 – 31 December 2014), (ii) total number of unique medicines dispensed in the baseline period based on ATC codes, and (iii) total number of unique medicines dispensed during the baseline period based on PBS item codes[15]. The distinction between ATC and PBS codes was made because different strengths or formulations of the same medicine have the same ATC code but different PBS codes; e.g. if a patient is dispensed two different strengths of the same medicine, this will be counted once in the total number of ATC medicines dispensed but twice in the total number of PBS medicines dispensed.

Statistical analysis

Primary analysis was performed in the DVA database. A baseline logistic regression model was calculated for mortality using age and gender as predictors. The comorbidity scores, individual comorbidities, and crude prescription counts were added to the baseline model separately. Age, comorbidity scores and crude prescription measures were included in the models as continuous variables assuming linear associations. Models using the individual comorbidities were developed with an indicator variable included for the presence (1) or absence (0) of each individual RxRisk category. The overall goodness-of-fit of each model was compared to the baseline model using the Akaike Information criterion (AIC)[16]. The model with the lowest AIC value is considered the best fit. The difference between the AIC

values of two models must be greater than 10 for one model to be considered superior to the other. Model discrimination was compared based on the c-statistic and the relative Integrated Discrimination Improvement (IDI) [17]. The value of the c-statistic can range from 0 to 1, with 1 indicating perfect prediction and 0.5 indicating chance predictions. A c-statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable[18]. Using 1000 bootstrap samples 95% confidence intervals were calculated for the c-statistics[9].

Internal validation of weighted scores

We used 10-fold cross-validation to internally validate the binary logistic regression model used to calculate the Rx-Risk category weights. This subsets the DVA cohort, using random sampling without replacement, into 10 equal folds. Each fold is a 10% subset of the DVA cohort. The training set consisted of 9 folds and was used to calculate Rx-Risk category weights. The calculated weights were then applied to the testing set (i.e. fold left out of training set). A binary logistic regression model of one- year mortality including age, gender and weighted Rx-Risk was built separately for the training set and testing set and the c-statistics recorded. This process was repeated ten times until each fold was used as the testing set once. This resulted in 20 c-statistics being calculated, 10 each on the training and testing set. The average c-statistic was recorded for each set.

Sensitivity analyses

Two sensitivity analyses were carried out. In the first sensitivity analysis we used the lower confidence limit of the odds ratio to determine the Rx-Risk category weights rather than the estimated odds ratio itself. We did this as some comorbidities are uncommon in this

population resulting in large confidence intervals. In the second sensitivity analysis we calculated the Rx-Risk category weights (based on the odds ratio) generated from 5000 bootstrap samples. For each Rx-Risk category the weight was calculated as the median of the 5000 weights for that category generated in each bootstrap sample. We did this sensitivity analysis to test the stability of the weights.

External Validation

To determine the external validity of the weights, the calculated Rx-Risk category weights derived from the DVA dataset were applied to the PBS cohort. The Akaike information criterion model fit and c-statistics were calculated to determine the validity of the model.

Results

Table 1 presents the ATC mapped Rx-Risk categories, derived empirical weights, and number of treated individuals in the DVA populations. The most frequent comorbidities identified by the Rx-Risk index in the DVA cohort were hypertension (53%), gastro-oesophageal reflux disease (GORD) (51%), hyperlipidaemia (50%), and conditions treated with antiplatelets (39%). In the DVA cohort of 135,406 people, with a mean age of 83 years (standard deviation (SD) 9.5) and 47% were men. The median unweighted Rx-Risk score was 5 (interquartile range (IQR) 3-7) and the median weighted Rx-Risk score was 3 (0-6).

The baseline model, comprising only age and gender, predicted one-year mortality moderately well in the DVA cohort (c-statistic=0.738, 95% Confidence Interval (CI) 0.734-0.742). The addition of Rx-Risk to the model increased the performance of the model: unweighted Rx-Risk c-statistic=0.751, (95% CI 0.747-0.754), IDI=14.0%, p-value<.0001;

weighted Rx-Risk c-statistic=0.786, (95% CI=0.782-0.789), IDI=65.6%, p-value<.0001; 43 individual comorbidities c-statistic=0.791, (95% CI=0.788-0.795), IDI=73.9%, p-value<.0001. The model including the 43 comorbidity indicator variables had the lowest AIC (75692), highest c-statistic (0.791), and the highest discrimination improvement (73.9%). The models including the weighted Rx-Risk score or 43 comorbidity measures were better predictors of one-year mortality than any of the crude prescription measures (Table 3). Results of the internal 10-fold cross validation were consistent with the main analysis with an average c-statistic of 0.785 achieved over the 10 testing datasets compared to a c-statistic of 0.786 in the primary analysis.

[Insert Table 3 here]

In the sensitivity analysis using the lower 95% confidence interval limit in the weighting algorithm we found a very similar performance with a c-statistic of 0.787 compared to the weighting algorithm using the estimated odds ratio (c-statistic 0.786). In the second sensitivity analysis in which the weights were calculated from 5000 bootstrap samples we found a similar c-statistic (0.786) compared to the primary analysis.

The PBS cohort consisted of 303,135 people, with an mean age of 75 years (standard deviation (SD) 7.4) and 45% were men. Similar to the DVA cohort, the most frequent comorbidities identified by the Rx-Risk index in the PBS cohort were hypertension (54%), hyperlipidaemia (52%) and gastro-oesophageal reflux disease (GORD) (41%). When the DVA derived Rx-risk category weights were applied to the PBS population we found a c-statistic of 0.833 (Table 3) showing good external validity.

Discussion

This paper presents the Rx-Risk index with each comorbidity category mapped to medicines at the ATC classification level using clinical expertise. The mapped index provides a resource for researchers working with health claims data utilising ATC codes or that have mappings to the ATC codes to calculate comorbidity, based on prescription medicine dispensing's in an outpatient population. We have shown that the updated Rx-Risk was highly predictive of one-year mortality in both the populations examined and is a valid measure of comorbidity in an outpatient population and is therefore likely to be useful in a range of observational data settings.

All forms of Rx-Risk predicted mortality better than just age and sex alone. The best results for predicting one-year mortality were achieved when modelling Rx-Risk as individual comorbidities or as a weighted score. The unweighted Rx-Risk score had similar performance to simple prescription medicine counts. Internal and external validation showed that the weighted index was predictive of one-year mortality within the veteran population and show good external validity when applied to a general population setting. These results suggest that the weighted RxRisk score is likely to be generalizable to other populations. Making the ATC map available to researchers will facilitate the use of the Rx-Risk in place of comorbidity estimated simply by prescription counts.

The Rx-Risk index has been updated accounting for the introduction of new medicines to the market, making this index a useful resource for researchers. The updated Rx-Risk has 46 comorbidities, however 3 (tuberculosis, and hepatitis B and C) were removed in the analysis stage as there were insufficient cases in the DVA cohort. A younger or larger sample may have allowed these comorbidities to be assessed. For consistency, these comorbidities were

also excluded from the analysis in the PBS cohort despite there being few but sufficient cases. The Rx-Risk index has been updated and mapped to ATC codes based on medicine availability in Australia; hence modifications may be required for use in other health systems.

The health care encounter inclusion criteria were not the same for both cohorts. The DVA cohort included people with a hospitalisation or GP visit, while the PBS cohort was limited to those with a prescription dispensing only. However, the difference across populations is small, as 96.7% of the DVA cohort had a medication dispensed in the six month selection period.

Comorbidity scores are often used in observational studies to reduce the potential for confounding. The advantage of these summary scores is that they simplify the inclusion of individual covariates for each comorbidity into a single summary score. This is a particular advantage when sample sizes are small or the outcome under study is rare. Our analysis demonstrated that the performance of the weighted RxRisk score performed as well as the model which included each individual comorbidity category. Additionally, including all individual comorbidities as indicator variables may not be appropriate in some studies, such as those looking at the effect of a particular treatment on an adverse event when the treatment itself is included in the construction of the comorbidity score. For example, when determining whether the risk of NSAIDS is associated with gastrointestinal bleeds, it would not be correct to adjust for inflammation/pain as an indicator as the medicines mapped to this comorbidity include NSAIDs. In this scenario it would be advisable to remove inflammation/pain as an indicator or use the weighted Rx-Risk score. Lastly, although the weighted RxRisk score performed well in the PBS data set, which suggests that the weights

have a good external validity, the Rx-Risk category weights derived in this study may not be applicable to all external populations. We limited our cohorts to patients over 65 years of age so factors that are predictors of mortality in this age group may not be predictors in a younger group.

Conclusion

The updated Rx-Risk comorbidity score is a valid measure of comorbidity and strongly predicted one-year mortality in an outpatient population. The weighted Rx-Risk score was found to be valid in an external population and may be useful in practice to adjust for confounding in observational studies using medication claims data.

Contributor statement:
Research area and study design: NP MK ER EER Data acquisition: NP MK JB; data analysis and interpretation: NP MK ER AKC LK; statistical analysis: NP MK; Mapping of the ATC codes to the RxRisk categories; JB LK EER. All authors drafted, edited and approved the final manuscript.

Competing Interests:
None declared for any author.

Funding:
This work was funded by the Australian Government Department of Veterans' Affairs (DVA) as part of the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) program. EER is supported by NHMRC GNT 1110139. DVA reviewed this manuscript before submission but had no role in the design or conduct of this research.

Data sharing Agreement:
Data are available through the Australian Government Department of Veterans' Affairs

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Table 1: List of Rx-Risk comorbidity categories, corresponding Anatomical Therapeutic Chemical (ATC) codes, and score weightings in relation to 1-year mortality risk in DVA and PBS data.

Rx-Risk comorbidity category	ATC codes	DVA Data	
		N (%)	Weights for Rx-Risk score
Alcohol dependecy	N07BB01-N07BB99	183 (0.1)	6
Allergies	R01AC01-R01AD60, R06AD02-R06AX27, R06AB04	16684 (12)	-1
Anticoagulants	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05	24863 (18)	1
Antiplatelets	B01AC04-B01AC30	52525 (39)	2
Anxiety	N05BA01-N05BA12, N05BE01	15615 (12)	1
Arrhythmia	C01AA05, C01BA01-C01BD01, C07AA07	14992 (11)	2
Benign prostatic hyperplasia	G04CA01-G04CA99, G04CB01, G04CB02[a]	9003 (7)	0
Bipolar disorder	N05AN01	231 (0.2)	-1
Chronic airways disease	R03AC02-R03DC03, R03DX05	33244 (25)	2
Congestive heart failure	C03DA02-C03DA99, C07AB02 - if PBS[d] item code is 8732N, 8733P, 8734Q, 8735R, C07AB07, C07AG02, C07AB12, C03DA04, (C03CA01–C03CC01 AND C09AA01–C09AX99, C09CA01–C09CX99)[b]	23975 (8)	2

Dementia	N06DA02-N06DA04, N06DX01	3868 (3)	2
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX18, N06AX21-N06AX26	43354 (32)	2
Diabetes	A10AA01-A10BX99	17550 (13)	2
Epilepsy	N03AA01-N03AX99	15484 (11)	0
Glaucoma	S01EA01-S01EB03, S01EC03-S01EX99	16262 (12)	0
Gastroesophageal reflux disease	A02BA01-A02BX05	69358 (51)	0
Gout	M04AA01-M04AC01	13723 (10)	1
Hepatitis B	J05AF08, J05AF10, J05AF11	7 (0.01)	NA
Hepatitis C	J05AB54, L03AB10, L03AB11, L03AB60, L03AB61, J05AE14, J05AE11-J05AE12, J05AX14, J05AX15, J05AX65, J05AB04	1 (0.0)	NA
Human immunodeficiency virus	J05AE01-J05AE10, J05AF12-J05AG05, J05AR01-J05AR99, J05AX07-J05AX09, J05AX12, J05AF01-J05AF07, J05AF09	42 (0.03)	0
Hyperkalaemia	V03AE01	197 (0.2)	4
Hyperlipidaemia	A10BH03[e], C10AA01-C10BX09	67690 (50)	-1
Hypertension	C03AA01-C03BA11, C03DB01, C03DB99, C03EA01, C09BA02-C09BA09, C09DA02-C09DA08, C02AB01-C02AC05, C02DB02-C02DB99, (C03CA01-C03CCO1 OR C09CA01-C09CX99)[c]	71867 (53)	-1

Hyperthyroidism	H03BA02, H03BB01	992 (1)	2
Hypothyroidism	H03AA01-H03AA02	13438 (10)	0
Irritable bowel syndrome	A07EC01-A07EC04, A07EA01-A07EA02, A07EA06, L04AA33	1132 (1)	0
Ischaemic heart disease: angina	C01DA02-C01DA14, C01DX16, C08EX02	16988 (13)	2
Ischaemic heart disease: hypertension	C07AA01-C07AA06, C07AA08-C07AB01, C07AB02 - if PBS[d] item code is not 8732N, 8733P, 8734Q, 8735R, C07AG01, C08CA01-C08DB01, C09DB01-C09DB04, C09DX01, C09BB02-C09BB10, C07AB03, C09DX03, C10BX03[f]	49947 (37)	-1
Incontinence	G04BD01-G04BD99	5554 (4)	0
Inflammation/pain	M01AB01-M01AH06	23510 (17)	-1
Liver failure	A06AD11, A07AA11	5034 (4)	3
Malignancies	L01AA01-L01XX41	7689 (6)	2
Malnutrition	B05BA01-B05BA10	16 (0.01)	0
Migraine	N02CA01-N02CX01	708 (1)	-1
Osteoporosis/Paget's	M05BA01-M05BB05, M05BX03, M05BX04, G03XC01, H05AA02	21448 (16)	-1
Pain	N02AA01-N02AX02, N02AX06, N02AX52, N02BE51	44035 (33)	3
Pancreatic insufficiency	A09AA02	433 (0.3)	0
Parkinsons	N04AA01-N04BX02	4237 (3)	3
Psoriasis	D05AA01-D05AA99,	1224 (1)	0

	D05BB01 D05BB02, D05AX02, D05AC01-D05AC51, D05AX52		
Psychotic illness	N05AA01-N05AB02, N05AB06-N05AL07, N05AX07-N05AX13	7714 (6)	6
Pulmonary hypertension	C02KX01-C02KX05, PBS[d] item code 9547L, 9605M	40 (0.03)	6
Renal disease	B03XA01-B03XA03, A11CC01-A11CC04, V03AE02, V03AE03, V03AE05	1816 (1)	6
Smoking cessation	N07BA01-N07BA03, N06AX12	1145 (1)	6
Steroid responsive disease	H02AB01-H02AB10	19106 (14)	2
Transplant	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02	102 (0.1)	0
Tuberculosis	J04AC01-J04AC51, J04AM01-J04AM99	0	NA

[a] Benign prostatic hyperplasia medicines are tested for gender - must be male. Females suffering from bladder obstructions can be prescribed medicines used to treat benign prostatic hyperplasia.
[b] Must have at least two medicines prescribed with one of those medicines having an Anatomical Therapeutic Chemical (ATC) code from C03CA01–C03CC01 and the other having an ATC code from either C09AA01–C09AX99 or C09CA01–C09CX99
[c] Can have medicine dispensed with an ATC code C03CA01–C03CC01 or C09AA01–C09AX99, but not both; as this would indicate chronic heart failure.
[d] Pharmaceutical Benefits Scheme
[e] Combination product for hyperlipidaemia and diabetes
[f] Combination product for hyperlipidaemia and ischaemic heart disease: hypertension

Table 2: Weighting algorithm used to score the Rx-Risk index.*

Odds ratio	P-value	Weighted Rx-Risk score
Any odds ratio	>0.10	0
<1	≤0.10	-1
1.0 ≤ and <1.2	≤0.10	1
1.2 ≤ and <1.4	≤0.10	2
1.4 ≤ and <1.6	≤0.10	3
1.6 ≤ and <1.8	≤0.10	4
1.8 ≤ and <2.0	≤0.10	5
≥2.0	≤0.10	6

*Weights are based on the size of odds ratio quantifying the probability of mortality in an outpatient population within one year, given treatment for a specified comorbidity.

Table 3: Comparison of different Rx-Risk scoring and modelling methods to predict one- year mortality in the DVA population and external validation using the PBS population.

	DVA				PBS			
Models	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**	**AIC[a]**	**Difference in AIC[b]**	**C-statistic[c] (95% Confidence Interval)**	**Relative IDI, p-value**
Base model (BM): age and sex	80538.5	-	0.738 (0.734, 0.742)	-	79527.9	-	0.761 (0.756, 0.766)	-
Rx-Risk measures								
BM + unweighted Rx-Risk	79420.1	1118.4	0.751 (0.747, 0.754)	14.0%, <.0001	77029.9	2498.0	0.796 (0.791, 0.800)	25.5%, <.0001
BM + DVA weighted Rx-Risk	76102.4	4436.1	0.786 (0.782, 0.789)	65.6%, <.0001	73143.8	6384.1	0.833 (0.829, 0.837)	92.0%, <.0001
BM + 43 comorbidity indicators	75692.2	4846.3	0.791 (0.788, 0.795)	73.9%, <.0001	71689.1	7838.8	0.845 (0.842, 0.849)	114.8%, <.0001
Crude measures								
BM + prescription count	79105.9	1432.6	0.755 (0.751, 0.759)	18.6%, <.0001	76762.8	2765.1	0.799 (0.795, 0.804)	31.4%, <.0001
BM + unique ATC[d] medicine count	78374.5	2164.0	0.762 (0.758, 0.766)	29.4%, <.0001	75369.1	4158.8	0.814 (0.810, 0.818)	50.0%, <.0001
BM + unique PBS Item Code[e] medicine count	78210.2	2328.3	0.764 (0.760, 0.768)	32.1%, <.0001	75108.8	4419.1	0.816 (0.812, 0.820)	55.8%, <.0001

[a] AIC: Akaike information criterion model. The model with the lowest AIC value is considered the best fit.
[b] AIC score compared to the AIC score of the base model. A model with a lower score of 10 (or more) is considered superior.

[c] Possible range 0-1, with 1 indicating perfect prediction and 0.5 indicating chance prediction. A c-statistic between 0.8–0.9 is generally considered as excellent, and between 0.7–0.8 acceptable.
[d] Anatomical Chemical Therapeutic classification system, count based on the number of unique ATC codes dispensed.
[e] Pharmaceutical Benefits Scheme, count based on the number of unique PBS item codes dispensed.