

RESEARCH ARTICLE

Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score)

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Abstract

Background

Adverse drug reactions (ADRs) are the major cause of medication-related hospital admissions in older patients living in the community. This study aimed to develop and validate a score to predict ADR-related hospitalization in people aged ≥ 65 years.

Methods

ADR-related hospitalization and its risk factors were determined using a prospective, cross-sectional study in patients aged ≥ 65 years admitted to two hospitals. A predictive model was developed in the derivation cohort ($n = 768$) and the model was applied in the validation cohort ($n = 240$). ADR-related hospital admission was determined through expert consensus from comprehensive reviews of medical records and patient interviews. The causality and preventability of the ADR were assessed based on the Naranjo algorithm and modified Schumock and Thornton criteria, respectively.

Results

In the derivation sample (mean [\pm SD] age, 80.1 ± 7.7 years), 115 (15%) patients were admitted due to a definite or probable ADR; 92.2% of these admissions were deemed preventable. The number of antihypertensives was the strongest predictor of an ADR followed by presence of dementia, renal failure, drug changes in the preceding 3 months and use of anticholinergic medications; these variables were used to derive the ADR prediction score. The predictive ability of the score, assessed from calculation of the area under the receiver operator characteristic (ROC) curve, was 0.70 (95% confidence interval (CI) 0.65–0.75). In the validation sample (mean [\pm SD] age, 79.6 ± 7.6 years), 30 (12.5%) patients' admissions were related to definite or probable ADRs; 80% of these admissions were deemed preventable. The area under the ROC curve in this sample was 0.67 (95% CI 0.56–0.78).

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Conclusions

This study proposes a practical and simple tool to identify elderly patients who are at an increased risk of preventable ADR-related hospital admission. Further refinement and testing of this tool is necessary to implement the score in clinical practice.

Introduction

Advancing age contributes to increased drug usage in older patients, which in turn is associated with an increased risk of adverse drug reactions (ADRs), causing significant morbidity and mortality [1]. The prevalence of ADRs in older outpatient clinic attendees ranges from 5–35% [2, 3]. ADRs are also one of the main reasons for hospitalization in older patients living in the community [4]. The proportion of all hospital admissions due to ADRs has ranged from 6–12% among older patients [1, 4–7]. While individual risk factors for ADRs have been identified [6, 8], health professionals are not able to easily identify elderly community-dwelling outpatients who are at high risk of being hospitalized due to an ADR. More than half of ADR-related hospitalizations are considered preventable [9].

In recent years, risk prediction models for ADRs in elderly patients have begun to emerge, offering practitioners a potential tool to assist clinical and therapeutic decision making, and facilitate targeting of additional resources toward this high-risk group [10, 11]. These tools were developed for use in secondary care hospital settings to help identify the risk of ADRs occurring during hospitalization. To our knowledge there is no prediction score available that has been developed for use in elderly patients with hospitalization due to ADR (as opposed to ADRs that arise during hospitalization) as the endpoint [12]. A tool developed that focussed on ADRs as a cause of hospitalization could potentially be used in primary care and at the point of hospital discharge to prioritize primary care-based medication management services to prevent ADR-related morbidity and mortality in patients at the highest risk of such events. We aimed to develop and validate a prediction model for ADR-related hospitalization in patients aged ≥ 65 years.

Methods

Derivation of a Score to Predict ADR-related Hospitalization

To develop the score [PADR-EC (Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) score], a prospective cross-sectional study was conducted at the Royal Hobart Hospital (RHH), which is the major public acute care hospital in Southern Tasmania. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee, and study participants provided their written informed consent to participate in the study. A convenience sample of all acute, unplanned, emergency admissions of patients aged ≥ 65 years admitted to medical wards over a period of 12 months (March 2014 to March 2015) were enrolled in the study. Patients were excluded if they were unwilling to participate, unable to be interviewed due to health or other reasons, or if their medical notes were not available for further investigation. The medical records of all consenting patients were reviewed within 48 hours of admission, and patients were interviewed as soon as practical after admission. Data collected included demographics, comorbidities, indicators of physical function and cognitive status, clinical diagnoses at admission, medications and medication changes prior to admission, previously documented ADRs, function in activities of daily living, social

supports and living status. Patients and/or their relatives who were interviewed provided information about alcohol consumption, smoking status, recent hospital admissions, recent drug changes, drug allergies, use of over-the-counter (OTC) and herbal medicines, use of dosage administration aids, ADR occurrence within the last 3 months, regular pharmacy visits, and receipt of a Home Medicines Review (HMR), where a pharmacist conducts an interview with the patient regarding their medications and provides a report back to the general practitioner.

Predictive Variables for ADR-related Hospitalization. Medications taken prior to admission were coded according to the Anatomical Therapeutic and Chemical codes [13]. Calculation of the number of medications was based on the number of active ingredients [6], where the active ingredients in combination products were also available as single-ingredient products. Clinical diagnoses and comorbidities were coded according to the International Classification of Primary Care, 2nd edition [14]. Comorbidity was measured using the Charlson comorbidity index (CCI) [15]. Renal failure was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m² [16]. Liver disease was defined as synthetic liver dysfunction or liver injury with raised transaminases greater than twice the normal range, or documented liver disease [17]. Anaemia was defined as a hemoglobin concentration below 120 g/L in women and below 130 g/L in men [18]. All comorbidities were defined as present if documented in the medical records. Functional independence was measured using the Barthel index [19]. Potentially inappropriate medications (PIMs) were identified using the updated Beers criteria [20]. Each class of PIMs within the Beers criteria was individually assessed. Recent drug changes prior to hospital admission were determined. Recent drug change was defined as addition of a new drug or deletion of an existing drug (excluding ‘when required’ medications) or a change in drug doses in the 3 months preceding the patient’s admission [21].

Identifying and Assessing the Presence of ADR-related Hospitalization. An ADR was defined as “a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” [22]. We assessed every consenting patient during the study period to determine if the admission had been caused by an ADR. The reasons for hospitalization are multifactorial in many cases [23], and therefore the determination of whether a certain drug/drugs may have caused or contributed to an acute admission was based on comprehensive review of medical records and interview with the patient/relatives about their medication usage, including recent changes to drug therapy. The patients were interviewed in presence of their family members and the response to specific questions (S1 Table) were again verified using electronic patient file or digital medical records which contains all patient previous admission/discharge details. Comprehensive review of medical records included detailed review of medical and nursing records, medical record notes from primary care when available, medication reconciliation notes from clinical pharmacists, and an assessment of laboratory and other relevant clinical investigations. Patients were categorized as having an ADR if the cause of admission was consistent with the known adverse effect profile of the drug (according to Australian Medicines Handbook, or UpToDate database)[24, 25], if there was a temporal relation with the start of drug therapy and if, after appropriate investigations, other causes were excluded [26]. The clinical description of each ADR and the potential drug cause was collected, and the causality, preventability and eventual outcome of the suspected ADR-related hospitalization were assessed. We also classified ADRs as Type A and Type B reactions, based on Rawlins and Thompson [27]. Type A reactions were defined as dose-dependent and predictable from the known pharmacologic action of the drug and Type B reactions if otherwise.

The Naranjo algorithm was used to assess the causality of the relation between drug use and hospitalization [28]. ADRs were classified as definite (9–12 points), probable (5–8 points), possible (1–4 points), or doubtful (0 points). Only definite and probable ADRs that provoked

hospitalization were considered for this study. ADRs observed during the hospital stay were excluded. The preventability of the ADR-related hospitalization was assessed using the modified Schumock and Thornton criteria [29, 30]. These criteria included (1) the drugs were not appropriate for the patient's condition, (2) the dose, frequency and route of administration were inappropriate for the patient's age, weight or disease state, (3) therapeutic drug monitoring or other necessary laboratory test was not performed, (4) the patient had a history of allergy or previous reaction to the administered drug, (5) a documented drug interaction was involved in the ADR, (6) a serum concentration above the therapeutic range was documented, (7) non-compliance was involved in the ADR or (8) a medication error was the cause of adverse reaction. The ADR-related hospitalization was considered to be preventable when it met any of these criteria.

All patients initially categorized as having an ADR-related admission, and a random selection of 10% of cases without a suspected ADR-related admission, were independently and blindly assessed by a senior clinical pharmacist for the presence and classification of an ADR-related admission. The primary researcher and the senior clinical pharmacist met to reach a consensus decision on the presence of an ADR-related admission and excluded doubtful cases. The cases thought to involve an ADR-related admission were also assessed blindly by the clinical pharmacist reviewer for causality, severity and preventability. This review process had been used previously in similar studies [26, 31, 32]. The screening process and identification of ADR-related hospital admissions is outlined in Fig 1.

Statistical analysis. The PADR-EC score was developed in a similar manner to that described by Onder et al [11]. Clinically relevant variables that are easily applied and practical for use in a primary care setting were considered. The chi-square test or Fisher's exact test were used to compare characteristics of those who experienced an ADR and those who did not. Variables identified as being associated with an ADR in the univariate analyses were entered into a binary logistic regression model. The variables with P values of <0.20 in the univariate analyses were candidates for inclusion in the binary logistic regression model, since more stringent significance levels can lead to the exclusion of potentially useful predictor variables [10, 33–35]. Multicollinearity between independent categorical variables was assessed using the phi coefficient [36]. When two variables had a phi coefficient ≥ 0.30 , the model was trialled with each variable independently and the variable with higher predictive ability was entered into the final model. Variables retained in the final model were used to compute the PADR-EC score. A score of 1 was assigned to variables with an odds ratio (OR) between 1.00 and 1.49; a score of 2 to those with an OR between 1.5 and 2.49; a score of 3 to those with an OR between 2.5 and 3.49; a score of 4 to those with an OR between 3.5 and 4.49 and a score of 5 to those with an OR between 4.5 and 5.49. The PADR-EC score was computed based on the sum of scores of individual variables. Receiver operator characteristic (ROC) curves were constructed and area under the curve (AUC) calculated to determine the predictive ability of the PADR-EC score. Analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois).

Validation study

In order to validate the PADR-EC score developed in the RHH sample (derivation stage), it was applied in a separate cohort of adults admitted to medical wards of the Launceston General Hospital (LGH). The LGH is the largest acute care facility and teaching hospital in the northern region of Tasmania. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee, and the study participants provided their written informed consent to participate in the study. Patients admitted to the LGH during the study period (September to December 2015) were enrolled according to the criteria discussed above. As before, data

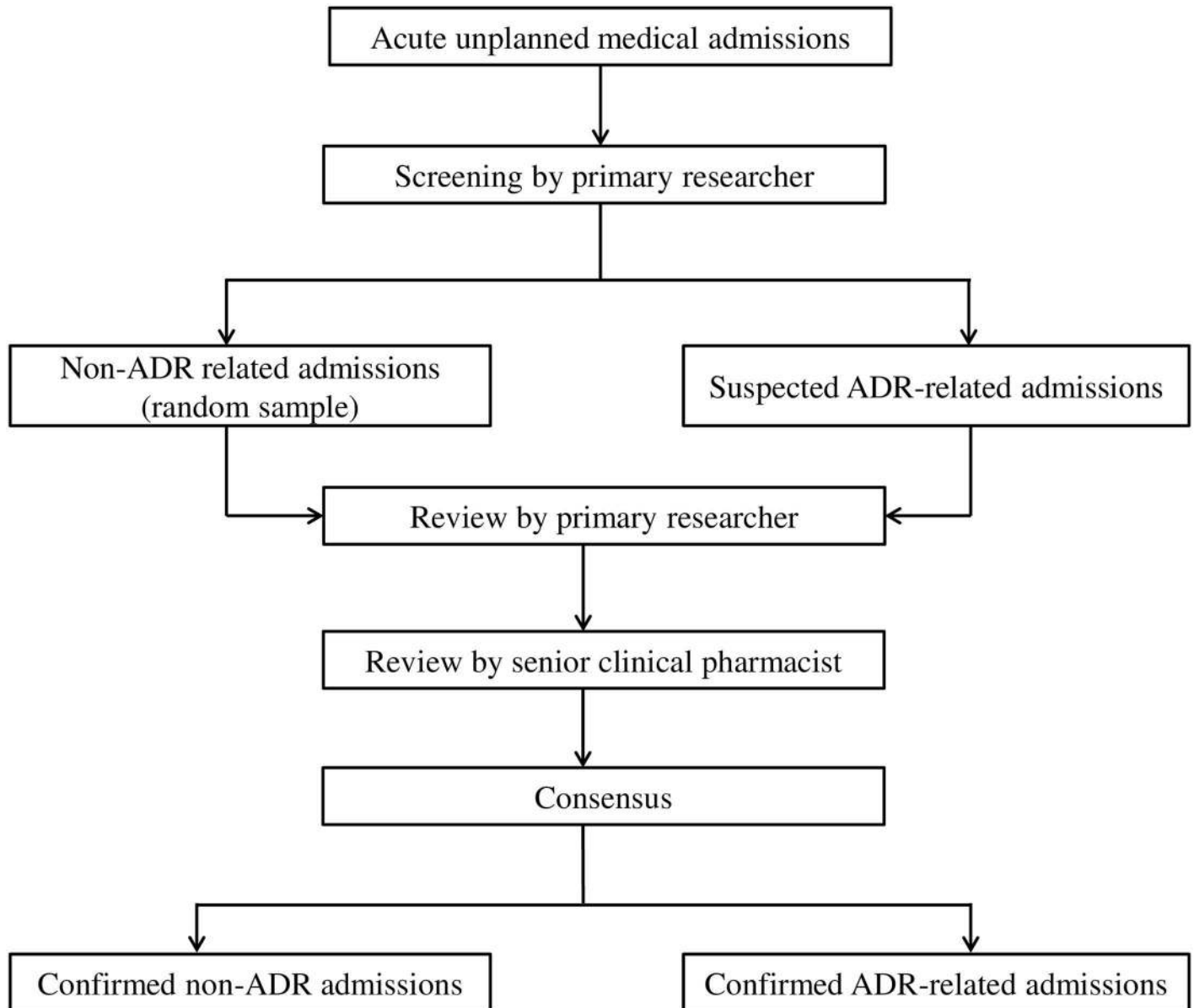


Fig 1. Diagram outlining the screening process of ADR-related hospital admission.

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for all variables were recorded for each patient, along with details of any suspected ADR-related admission. To evaluate the predictive ability of the PADR-EC score, ROC curves were constructed and AUC calculated.

Results

Derivation of the PADR-EC Score

Over the 12-month study period, there were 5,027 acute unplanned medical admissions in patients aged ≥ 65 years at the RHH. Of the 1,271 (25%) patients screened during the study period, 503 (39.6%) were excluded either due to their unwillingness to consent (130 patients), or an inability to participate due to the severity of their medical condition, hearing impairment

Table 1. Characteristics of the study populations in derivation and validation cohort.

| Characteristics | Derivation stage (n = 768) | Validation stage (n = 240) |
|---|----------------------------|----------------------------|
| Age in years (mean ± SD) | 80.1 ± 7.7 | 79.6 ± 7.6 |
| Gender (n, %), Female | 401 (52.2) | 137 (57.1) |
| Number of medications before hospital admission (mean ± SD) | 10.8 ± 5.2 | 9.9 ± 4.8 |
| Number of comorbidities (mean ± SD) | 5.5 ± 2.4 | 6.0 ± 2.5 |
| Living status (n, %) | | |
| Alone | 308 (40.1) | 101 (42.1) |
| With family or friends | 433 (56.4) | 135 (56.3) |
| Nursing home | 27 (3.5) | 4 (1.7) |
| Comorbidities (n, %) | | |
| Dementia | 54 (6.4) | 15 (6.3) |
| Heart failure | 136 (16.2) | 52 (21.7) |
| Renal failure | 406 (48.4) | 125 (52.1) |
| Cerebrovascular disease | 141 (16.8) | 37 (15.4) |
| Diabetes | 236 (28.1) | 69 (28.8) |
| Chronic obstructive pulmonary disease | 208 (24.8) | 89 (37.1) |
| Cancer | 179 (21.3) | 67 (27.9) |
| Anemia | 327 (39) | 116 (48.3) |
| Liver disease | 22 (2.6) | 11 (4.6) |
| Depression | 94 (11.2) | 35 (14.6) |
| Hyperlipidemia | 240 (28.6) | 74 (30.8) |
| Ischemic heart disease | 160 (19.1) | 55 (22.9) |
| Vascular disease | 309 (36.8) | 90 (37.5) |

Abbreviations: SD, standard deviation.

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or low vision (373 patients). In total, 768 patients were included in the RHH cohort for final analysis. The characteristics of the study populations at the RHH and LGH are summarized in [Table 1](#).

There was a consensus between the two expert reviewers in the majority of cases and, overall, 115 patients (15.0%) were judged as being admitted due to ADRs. There were 17 doubtful cases that were not classified as ADR-related admissions and were added to the control group (n = 653). There were 9 (5.8%) definite and 106 (69.3%) probable ADRs based on the Naranjo algorithm. Most of the ADR-related hospitalizations were considered preventable (106, 92.2%) and all ADRs were classified as Type A reactions except one which was considered as a Type B reaction. As seen in [Table 2](#), univariate analysis identified that PIMs (anticholinergics, antiarrhythmics, benzodiazepines), PIMs use in dementia or cognitive impairment, hospital admission in the preceding month, hospital admission in the preceding 3 months, drug changes in the preceding 3 months, 9 or more regular medications, 7 or more comorbidities, renal failure, dementia, heart failure, anemia, vascular disease, Charlson comorbidity score ≥ 6 , use of alcohol and age ≥ 85 years were associated with an increased risk of ADR-related hospital admission ($P \leq 0.20$). Specific drug classes contributing to the risk of ADR-related admission included antihypertensives (1–2, ≥ 3), angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, drugs of narrow therapeutic index (digoxin, amiodarone, theophylline, phenytoin, carbamazepine and sodium valproate), psycholeptics, benzodiazepines, tricyclic antidepressants, diuretics and tricyclic antidepressants or psycholeptics. The antihypertensives included α_2 -adrenergic agonists, α_1 -adrenoreceptor antagonists, beta-blockers, calcium channel blockers, diuretics, agents acting on the renin-

Table 2. Characteristics of patients experiencing adverse drug reaction-related and non-adverse drug reaction-related hospital admissions at the Royal Hobart Hospital (n = 768).

| Variable | Number (%) No ADR (n = 653) | Number (%) ADR (n = 115) | P Value |
|--|--------------------------------|-----------------------------|---------|
| Age (years) | | | |
| 65–84 | 454 (69.5) | 70 (60.9) | 0.07* |
| ≥85 | 199 (30.5) | 45 (39.1) | |
| Gender | | | |
| Male | 316 (48.4) | 51 (44.3) | 0.42 |
| Female | 337 (51.6) | 64 (55.7) | |
| Drug-related variables | | | |
| Use of OTC medications | 275 (42.1) | 45 (39.1) | 0.55 |
| Use of herbal medications | 156 (23.9) | 24 (20.9) | 0.48 |
| Drug changes in the preceding 3 months | 304 (46.6) | 70 (60.9) | 0.01* |
| Number of medications | | | |
| 0–8 | 245 (37.5) | 32 (27.8) | 0.05* |
| ≥9 | 408 (62.5) | 83 (72.2) | |
| Inappropriate medications (Therapeutic category/drug) | | | |
| Anticholinergics | 57 (8.7) | 21 (18.3) | 0.002* |
| Benzodiazepines | 128 (19.6) | 29 (25.2) | 0.17* |
| Antiarrhythmics | 18 (2.8) | 8 (7) | 0.04* |
| Digoxin | 10 (1.5) | 2 (1.7) | 0.70 |
| Metoclopramide | 14 (2.1) | 4 (3.5) | 0.33 |
| Inappropriate medications (Disease) | | | |
| Heart failure | 10 (1.5) | 1 (0.9) | 1.00 |
| Dementia or cognitive impairment | 14 (2.1) | 8 (7) | 0.01* |
| Disease-related variables | | | |
| Charlson Comorbidity Index | | | |
| 0–5 | 344 (52.7) | 52 (45.2) | 0.14* |
| ≥ 6 | 309 (47.3) | 63 (54.8) | |
| ≥7 Comorbidities | 206 (31.5) | 51 (44.3) | 0.01* |
| Cerebrovascular diseases | 117 (17.9) | 24 (20.9) | 0.45 |
| Diabetes | 200 (30.6) | 36 (31.3) | 0.89 |
| Anemia | 270 (41.3) | 57 (49.6) | 0.10* |
| Depression | 81 (12.4) | 13 (11.3) | 0.74 |
| Acute cognitive impairment | 41 (6.3) | 5 (4.3) | 0.42 |
| Dementia | 42 (6.4) | 12 (10.4) | 0.12* |
| Renal failure † | 323 (49.7) | 83 (72.8) | <0.001* |
| Liver disease | 18 (2.8) | 4 (3.5) | 0.56 |
| Heart failure | 108 (16.5) | 28 (24.3) | 0.04* |
| COPD | 176 (27) | 32 (27.8) | 0.85 |
| Cancer | 156 (23.9) | 23 (20) | 0.36 |
| Hyperlipidemia | 204 (31.2) | 36 (31.3) | 0.99 |
| Ischemic heart disease | 133 (20.4) | 27 (23.5) | 0.45 |
| Vascular disease | 254 (38.9) | 55 (47.8) | 0.07* |
| Variables related to drug classes | | | |
| Drugs of narrow therapeutic index | 158 (24.2) | 38 (33) | 0.05* |
| Antithrombotics | 444 (68) | 85 (73.9) | 0.21 |
| Antihypertensives | | | |

(Continued)

Table 2. (Continued)

| Variable | Number (%) | Number (%) | P Value |
|--|------------------|---------------|---------|
| | No ADR (n = 653) | ADR (n = 115) | |
| 0 | 131 (20.1) | 6 (5.2) | |
| 1–2 | 328 (50.2) | 51 (44.3) | <0.001* |
| ≥3 | 194 (29.7) | 58 (50.4) | |
| ACEIs or ARBs | 357 (54.7) | 77 (67) | 0.01* |
| Calcium channel blockers | 172 (26.3) | 34 (29.6) | 0.47 |
| Cardiac glycosides | 69 (10.6) | 15 (13) | 0.43 |
| Beta-blockers | 223 (34.2) | 52 (45.2) | 0.02* |
| Drugs used in diabetes | 156 (23.9) | 29 (25.2) | 0.76 |
| NSAIDs | 27 (4.1) | 6 (5.2) | 0.60 |
| Opioids | 199 (30.5) | 41 (35.7) | 0.27 |
| Psycholeptics | 158 (24.2) | 36 (31.3) | 0.11* |
| Antipsychotics | 37 (5.7) | 9 (7.8) | 0.37 |
| Benzodiazepines | 137 (21) | 32 (27.8) | 0.10* |
| Tricyclic antidepressants | 57 (8.7) | 15 (13) | 0.14* |
| Tricyclic antidepressants or psycholeptics | 197 (30.2) | 46 (40) | 0.04* |
| Antiplatelets | 320 (49) | 61 (53) | 0.42 |
| Diuretics | 309 (47.3) | 80 (69.6) | <0.001* |
| Antibacterials | 94 (14.4) | 14 (12.2) | 0.53 |
| Anticoagulants | 140 (21.4) | 30 (26.1) | 0.27 |
| Other variables | | | |
| Admission in preceding month | 159 (24.3) | 38 (33) | 0.05* |
| Admission in preceding 3 months | 269 (41.2) | 55 (47.8) | 0.18* |
| Use of dosage administration aid | 259 (39.7) | 45 (39.1) | 0.91 |
| Use of generics † | 345 (60.5) | 62 (62.6) | 0.69 |
| Use of alcohol | 241 (36.9) | 35 (30.4) | 0.18* |
| Smokers | 72 (11) | 9 (7.8) | 0.30 |
| Presence of ADR within 3 months ‡ | 106 (16.5) | 22 (20.2) | 0.35 |
| Previous ADR † | 389 (59.8) | 65 (57) | 0.57 |
| Regular pharmacy visits | 582 (89.1) | 105 (91.3) | 0.48 |
| HMR in the preceding 3 months | 41 (6.3) | 5 (4.3) | 0.42 |
| Assistance required with ≥1 activity of daily living | 433 (66.3) | 83 (72.2) | 0.22 |
| Albumin <3.5 g/dL | 293 (44.9) | 54 (47) | 0.68 |
| Falls | 38 (5.8) | 6 (5.2) | 0.80 |

Abbreviations: OTC, over-the-counter; COPD, chronic obstructive pulmonary disease; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs; ADR, adverse drug reaction; HMR, Home Medicines Review.

*P value ≤0.20.

‡ 4 participants had missing values.

† 99 participants had missing values.

‡ 17 participants had missing values.

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angiotensin system and vasodilators. Fixed-dose antihypertensive combination therapy, including triple therapy, was used in 12% (n = 95) of patients. The PIMs (anticholinergics) included antihistamines (chlorpheniramine and promethazine), antispasmodics (hyoscyamine products and atropine products) and tertiary tricyclic antidepressants (amitriptyline, imipramine and doxepin >6 mg/day). When variables were excluded due to multicollinearity, the

Table 3. Binary logistic regression of factors associated with adverse drug reaction-related hospital admission in the derivation study at the Royal Hobart Hospital (n = 768).

| Variable | Adjusted OR (95% CI) | P value |
|--|----------------------|---------|
| Age ≥85 years | 1.33 (0.86–2.06) | 0.20 |
| Drug changes in the preceding 3 months | 1.54 (1.00–2.37) | 0.05 |
| Anemia | 1.08 (0.70–1.65) | 0.74 |
| Renal failure | 1.97 (1.22–3.17) | 0.01 |
| Drugs of narrow therapeutic index | 1.15 (0.73–1.81) | 0.55 |
| Dementia | 2.44 (1.17–5.10) | 0.02 |
| Admission in preceding month | 1.31 (0.82–2.07) | 0.26 |
| Number of comorbidities ≥7 | 1.07 (0.69–1.66) | 0.76 |
| Number of antihypertensives | | |
| 1–2 | 3.00 (1.22–7.38) | 0.02 |
| ≥3 | 4.75 (1.89–11.93) | 0.001 |
| Anticholinergics | 2.09 (1.16–3.75) | 0.01 |
| Psycholeptics | 1.24 (0.78–1.98) | 0.36 |
| Use of alcohol | 0.80 (0.51–1.25) | 0.32 |

Abbreviations: CI, confidence interval; OR, odds ratio.

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variables retained in the model were hospital admission in the preceding month, drug changes in the preceding 3 months, 7 or more comorbidities, renal failure, dementia, drugs of narrow therapeutic index, antihypertensives (1–2, ≥3), anemia, PIMs (anticholinergics), psycholeptics, age ≥85 years and use of alcohol. Binary logistic regression retained drug changes in the preceding 3 months, renal failure, dementia, antihypertensives (1–2, ≥3), and PIMs (anticholinergics) as significant predictors of ADR-related hospital admission (Table 3). These variables were assigned scores based on their respective ORs (Table 4).

Drug changes in the preceding 3 months, renal failure, dementia and PIMs (anticholinergics) were scored at 2 points and antihypertensives received a score of 3 points (1–2 antihypertensive agents) or 5 points (≥3 antihypertensives). The range of scores was from 0 to 11, with a median of 5 (IQR 5). The area under the ROC curve, which assesses the ability of the risk score to predict ADR-related hospitalization in the whole population, was 0.70 (95% CI 0.65–0.75) (S1 Fig). A score cut off at 6 provided a good balance between sensitivity (72.2%) and specificity (58.0%). The risk of patients having an ADR-related hospitalization was more than three times higher in those who scored ≥6 compared to those who scored <6 (OR 3.59 [95% CI 2.32–5.55]).

Table 4. Variables included in the risk score.

| Variable | OR (95% CI) | Points |
|--|-------------------|--------|
| Drug changes in the preceding 3 months | 1.54 (1.00–2.37) | 2 |
| Renal failure | 1.97 (1.22–3.17) | 2 |
| Dementia | 2.44 (1.17–5.10) | 2 |
| Number of antihypertensives | | |
| 1–2 | 3.00 (1.22–7.38) | 3 |
| ≥3 | 4.75 (1.89–11.93) | 5 |
| Anticholinergics | 2.09 (1.16–3.75) | 2 |

Abbreviations: CI, confidence interval; OR, odds ratio.

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Validation study

Over the study period of 4 months, 518 patients were screened at the LGH. Of these, 123 patients were excluded due to their unwillingness to consent and 155 patients could not be recruited due to the severity of their medical condition. In total, 240 patients were included in the LGH cohort for the validation of the PADR-EC score. Definite (2, 5.2%) and probable (28, 73.7%) ADR-related hospital admissions were observed in 30 patients (12.5%) in this sample. The patients' characteristics are summarized in [Table 1](#).

The majority of the ADR-related hospitalizations were considered preventable (24, 80%). When the PADR-EC score was applied to the LGH data set, the AUC was 0.67 (95% CI 0.56–0.78) ([S1 Fig](#)). A score cut off at 6 provided a good balance between sensitivity (63%) and specificity (63%). In the LGH data set, patients who scored ≥ 6 had almost three times the risk of ADR-related hospitalization compared to those scoring < 6 (OR 2.92 [95% CI 1.32–6.46]). The percentage increase of ADR-related hospitalization with respect to the cut-off score ≥ 6 in both the RHH and LGH data set is outlined in [Fig 2](#).

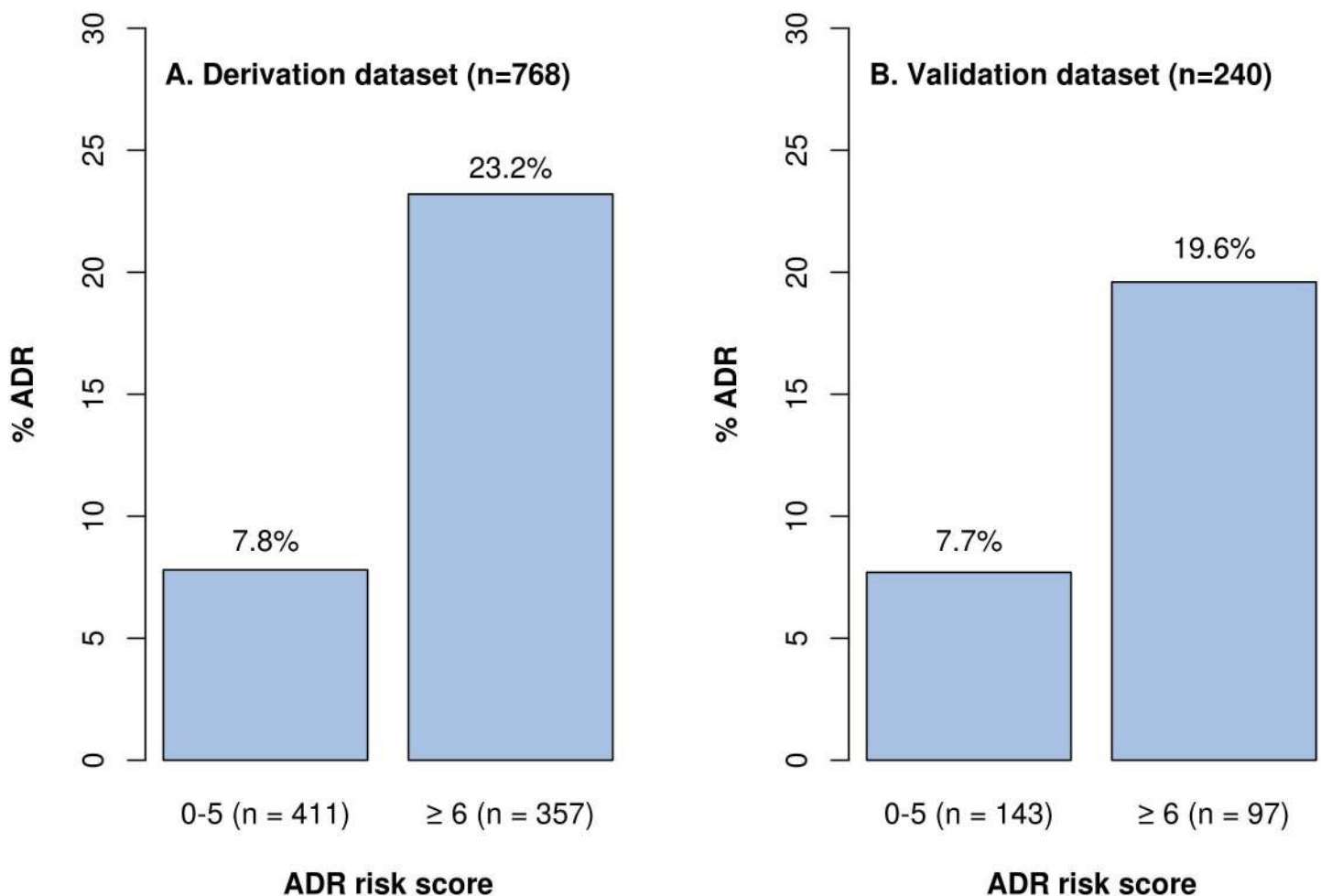


Fig 2. Adverse drug reaction rate according to risk score. (A) The adverse drug reaction rate at cut off score at 6 in the derivation dataset at the Royal Hobart Hospital. (B) The adverse drug reaction rate at cut off score at 6 in the validation dataset at the Launceston General Hospital.

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Discussion

We developed and validated a simple and robust approach to identifying community-dwelling elderly patients at risk of hospitalization due to ADRs. To our knowledge, this is the first study to develop such a score. This score has the potential to assist healthcare practitioners to identify those elderly patients for whom intervention may reduce the risk of ADRs and subsequent hospitalization. In addition, patients could be stratified at hospital discharge according to their risk of subsequent admission of an ADR, and appropriate medication management services provided accordingly post-discharge.

The variables we identified as independent predictors of ADRs in the elderly have been described in previous studies [37–40]. Drug changes in the preceding 3 months were found to predict ADR-related admission in the present study. Changes in medications such as using a different dose, discontinuing therapies, and taking new drugs were observed in the majority of elderly patients after hospital discharge in a follow-up study [21] and clinically significant changes to medicines or treatment plans within the last 3 months were found to be a risk factor for medication-related problems [37, 41]. ADRs attributed to medication changes occurred in 20% of patients during transfer from hospital and nursing home in a study conducted in United States [42]. Renal failure was found to be another significant predictor of ADR-related admission in the present study. The relation between renal insufficiency and ADRs is well documented in the literature [43, 44]. Impaired renal function (OR 2.6; 95% CI 1.6–4.2) was found to be a major determinant of preventable medication-related hospital admission in a prospective multicentre study [45]. Renal failure was also found to be predictor of ADRs in the GerontoNet ADR score study (OR 1.2; 95% CI 0.9–1.5) as well as in a prospective study of elderly individuals who presented to an emergency department (OR 1.5; 95% CI 1.1–2.2) [11, 46]. In the present study, we found elderly patients with renal failure were twice as likely to be hospitalized due to ADRs. The presence of dementia was identified as another independent predictor of ADR-related hospitalization. The prevalence of ADRs in elderly patients with dementia was 5.0% in another study; half of the ADRs were due to use of psychotropic and anti-dementia drugs [47]. Drug-related problems appeared to be responsible for the majority of hospitalizations among old people with dementia and the most common drug-related problem was an ADR (18.7%) in a recent study [32].

PIMs are significantly associated with ADRs and subsequent hospital admission [12]. Inappropriate medications were associated with a two-fold increased risk of an ADR in the elderly in a prospective study [17]. Among the PIMs, use of anticholinergics was found to be the predictor of ADR-related hospital admission in the present study. The prevalence of exposure to anticholinergic medicines in the elderly has ranged from 22.8% to 55.9% [48]. The use of drugs with anticholinergic adverse effects is often inappropriate in older patients aged ≥ 65 years [49]. Many age-related and disease-related conditions may predispose older patients to ADRs related to anticholinergic drugs [50]. These drugs have many effects in the elderly, ranging from dry mouth and constipation to confusion, delirium and severe cognitive impairment [51]. Another important predictor of ADR-related admission in the present study was the use of multiple antihypertensives. Approximately 70% of patients with hypertension require two or more drugs to achieve their target blood pressure [52]. The use of multiple antihypertensives in elderly patients is a frequent cause of hospital admission [53]. Antihypertensives were found to be one of the most frequently implicated drugs in causing ADRs and the risk is higher with combination therapy and in patients receiving multiple antihypertensive drugs [54–56]. In a community-based randomized open label trial [57] there was a significant increase in dizziness reported with combination antihypertensive therapy. The prevalence of orthostatic hypotension has been reported to be between 35% and 65% for the elderly and is mainly associated with the use of antihypertensive medications [58–60].

This study found that almost 15% of admissions in the elderly were due to ADRs. Meta-analysis of observational studies in the elderly reported a similarly high rate (16.6%) of ADR-related hospitalization [61]. The PADR-EC score has a predictive ability of 70% to discriminate patients who are at high risk of ADR-related hospitalization and those who are not. The subsequent validation study found a predictive ability of 67%. The sensitivity of the score was 72% in the derivation cohort, which indicates the ability of the score to correctly classify a patient as a victim of preventable ADR-related admission. Importantly, the expert reviewers also identified that the majority of ADR-related admissions were preventable. The predictive ability of the risk score could therefore be utilized to identify ADRs which may be prevented by monitoring of patients' drug therapy, addressing inappropriate dosing, aiding patient compliance with therapy and managing drug interactions to avoid subsequent admission. To our knowledge, there is no previously developed ADR prediction tool for use in primary care to which to compare the present study findings; however, the score performed comparably to validated ADR prediction tools used to predict ADR risk in hospitalized patients, such as those developed by Onder et al. (predictive ability of 71%) [11] and Tangiisuran et al. (74%) [10]. While there are tools available to predict the risk of emergency admission to hospital [62–64], our tool was developed to focus specifically on the risk hospitalisation due to an ADR to enable primary health care professionals to better direct medication management services to prevent ADRs.

The PADR-EC score consists of five clinical variables that are easy to apply and practical to assess in elderly patients. The development of this tool may assist general practitioners or primary care physicians in identifying older patients who have a high risk of ADRs and subsequent emergency hospital admissions [12]. This is particularly important considering that it may be challenging for healthcare practitioners to easily identify patients who are at risk of hospitalization due to ADRs, partly due to significant time pressures in office-based practice [65]. The PADR-EC score could potentially be integrated into prescribing software to alert primary care physicians to their patients' risk of ADRs and prompt appropriate preventive measures. Such preventive measures may include medication review, avoiding use of PIMs, computer-based prescribing systems and comprehensive geriatric assessment [66], as well as deprescribing (withdrawal of an inappropriate medication) [67] and avoiding unnecessary polypharmacy when drugs are no longer efficacious or beneficial, or when safer alternatives exist [68]. The PADR-EC score could also be applied at hospital discharge to identify older patients who are at higher risk of admission for ADRs to facilitate post-discharge medication management review services and/or closer monitoring by relevant health professionals to prevent subsequent hospitalization. Thus, application of PADR-EC score could potentially play a role in reducing the risk of ADR-related hospitalizations in the elderly.

Limitations include the score's specificity of 58%, resulting in a chance of incorrectly labeling patients as 'having an ADR risk' who may not be at risk (false positives). The validation sample had almost equal or slightly less discriminatory power compared to the derivation sample, suggesting that further refinement and testing of the PADR-EC score is required before implementing the score in clinical practice. The time restraints did not allow us to validate the tool further in a community setting to follow the patients in primary care to observe an ADR related hospital admission outcome versus other disease related outcomes. However, the variables used to derive the score only used patient information before hospital admission and all the patients recruited in the study were primary care patients. There were inherent limitations in assessing the predictor 'drug changes in the preceding 3 months', as this could have potentially been influenced by incomplete records. We minimized this issue by interviewing the patient/relatives about their medication usage, including recent changes to drug therapy, and comprehensively reviewing medical records and, importantly, medication reconciliation reports from clinical pharmacists. Some of the variables arose from patient interviews and thus

could be a subject to recall bias; this was limited by conducting interviews in the presence of family members. We could not recruit some patients due to difficulty in getting the consent mainly due to their severity of disease. Thus, obtaining consent was the limiting step, and a retrospective study could have included these additional patients, although such a study would lose the ability to obtain information through interview. The degree of generalizability of the proposed model is restrained by convenience sampling, however the large sample size used in the study may have reduced the sampling error and hence, may not have affected the applicability of the proposed model. We cannot assess the time frame for ADR occurrence after identifying patients at risk. Hence, further studies are required to address this issue in order to predict ADRs and subsequent admission in a timely fashion. Further investigation is needed to determine the absolute risk for people identified as being at high-risk of ADRs using this score, and whether interventions in these patients by health care professionals are able to reduce this risk.

Conclusion

We propose a simple, efficient and practical tool to identify elderly patients living in the community who are at increased risk of ADR-related hospitalization. The PADR-EC score was developed and externally validated reasonably in a cohort of elderly subjects admitted to two participating centres. It has the potential to be easily used, mainly by primary care physicians to identify elderly patients vulnerable to ADRs, and target interventions to prevent subsequent hospitalization. Even though further refinement and testing of this tool is necessary before implementing the score in clinical practice, this tool could provide a useful starting point to predict risk for ADR-related hospitalization in the elderly. Further studies are required to assess the clinical utility of this tool in different settings and populations.

Supporting Information

S1 Fig. Receiver operator characteristic curve for the derivation dataset (A) and the validation dataset (B). The area under the curve are 0.70 (95% CI 0.65–0.75) and 0.67 (95% CI 0.56–0.78) for the derivation and validation datasets respectively.
(TIF)

S1 Table. Questionnaires to participants.
(DOCX)

Author Contributions

Conceptualization: LB NP LC BB CC.

Data curation: NP LB.

Formal analysis: NP LB LC BB CC GP.

Investigation: NP LB LC BB CC MC.

Methodology: NP LB LC BB CC MC GP RC.

Supervision: LB LC BB CC.

Writing – original draft: NP.

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