Hospitalization in older patients due to adverse drug reactions – the need for a prediction tool

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Abstract: Adverse drug reactions (ADRs) represent a major burden on society, resulting in significant morbidity, mortality, and health care costs. Older patients living in the community are particularly susceptible to ADRs, and are at an increased risk of ADR-related hospitalization. This review summarizes the available evidence on ADR-related hospital admission in older patients living in the community, with a particular focus on risk factors for ADRs leading to hospital admission and the need for a prediction tool for risk of ADR-related hospitalization in these individuals. The reported proportion of hospital admissions due to ADRs has ranged from 6% to 12% of all admissions in older patients. The main risk factors or predictors for ADR-related admissions were advanced age, polypharmacy, comorbidity, and potentially inappropriate medications. There is a clear need to design intervention strategies to prevent ADR-related hospitalization in older patients. To ensure the cost-effectiveness of such strategies, it would be necessary to target them to those older individuals who are at highest risk of ADR-related hospitalization. Currently, there are no validated tools to assess the risk of ADRs in primary care. There is a clear need to investigate the utility of tools to identify high-risk patients to target appropriate interventions toward prevention of ADR-related hospital admissions.

Keywords: adverse drug reactions, hospital admission, prediction, older patients, primary care, risk factors

Introduction
Medication-related adverse events (AEs) in general practice represent an important cause of morbidity and are thought to cause between 10% and 30% of all hospital admissions in older patients.1,2 These AEs are defined as “any untoward medical occurrences that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment”.3 Among these AEs, adverse drug reactions (ADRs) represent a major burden, causing significant morbidity, mortality, and health care costs.4,5 The World Health Organization defines an ADR as any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and drug abuse.4,5 ADRs can be assessed as severe, moderate, or mild reactions.6 A severe ADR is life-threatening, causing permanent damage or requiring intensive care. Moderate ADRs require hospital admission, a change in therapy, or specific treatment. In a meta-analysis of prospective studies, 1,00,000 deaths per year could be attributed to ADRs in the USA, which highlights the seriousness and extent of the problem.6 Furthermore, a Swedish study estimated that 3.1% of deaths in the general population (including subjects who died in and outside hospitals) were attributed to ADRs.9

Older patients are particularly susceptible to ADRs due to multiple comorbidities, cognitive and functional impairment, a high prevalence of multiple
medications (polypharmacy), and age-related changes in pharmacokinetics and pharmacodynamics. A significant consequence of ADRs in older adults living in the community is hospitalization and its related costs. These patients then become susceptible to hospitalization-related complications, such as cardiovascular and neurological disorders, nosocomial infections, and deconditioning. It may be challenging for primary care physicians (or general practitioners [GPs]) to easily identify patients who are at risk of hospitalization due to ADRs, partly due to significant time pressures in office-based practice. This narrative review explores our current understanding of ADR-related hospitalization in older patients, with a particular focus on risk factors and the need for a prediction tool for ADR-related hospitalization for utilization in community settings.

**ADR-related hospitalization in older patients – how significant is the problem?**

Based on a retrospective cohort study in a veteran population (median age 81 years), the overall proportion of potentially preventable medication-related hospitalizations was 20.3% over a 5-year period. ADRs were the most common cause, accounting for one-third of hospitalizations based on a study by Chan et al. Data collected from GP encounters in 2003–2004 in Australia indicated that ADRs represented the most common adverse drug event (ADE) in the community (72%), of which the majority were moderate or severe and required hospitalization. The proportion of all hospital admissions due to ADRs has ranged from 6% to 12% among older patients. Also, one study conducted in Canada found that emergency department visits and hospital admissions due to ADRs in older patients cost an estimated US$35.7 million annually.

**Severity, causality, and avoidability of ADR-related hospitalization in older patients**

ADR-related hospitalization can lead to fatal outcomes and increased length of stay in older patients. The severity of ADR-related admissions was assessed in a prospective study, in which 18.6% of cases were identified as severe ADRs. The most severe ADRs were related to hemorrhage and other hematological disorders, and acute renal failure. Most of the ADRs causing hospital admission in older patients were type A reactions, which are predictable from the known pharmacology of the drug, whereas type B reactions (bizarre or non-dose-related reactions) accounted for only 8.1% based on a cross-sectional study.

Since ADRs are a major cause of morbidity and mortality, it is important to demonstrate a causal relationship between the drug and the adverse clinical event. Furthermore, it is often difficult to decide if an adverse clinical event is an ADR or due to deterioration in the patient’s disease state. Therefore, causality assessment is used to determine the likelihood that a drug caused a suspected ADR. The most widely used and generally accepted causality assessment scales in clinical practice are the probability scales developed by the World Health Organization Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden) and the Naranjo ADR Probability Scale. These scales use inter-rater agreement scores, which are superior to subjective clinical judgment. However, they can be difficult to interpret in the context of older patients with multiple comorbidities and medications. Based on different studies, the majority of ADRs in older adults leading to hospital admission were either probable or possible based on causality assessments. Definite or certain ADRs accounted for only 4% and 6.8%, respectively, in some studies. While some ADR-related hospitalizations are unavoidable, even with the most extraordinary precautions (eg, immunological reactions), more than half of hospital admissions for ADRs are preventable. Potentially avoidable ADRs leading to hospital admission in older adults could be due to improper dosage, missed contraindications and drug interactions, or reexposure of patients who had known drug allergies. ADRs can be classified into definitely avoidable, possibly avoidable, unavoidable, and unclassifiable based on the Halls criteria. Among the ADRs causing hospital admission in older patients, most were either definitely or possibly avoidable, with only 18.6%–28% of cases considered unavoidable.

**Most common ADRs causing hospitalization in older patients**

Advancing age can contribute to a significant increase in sensitivity to particular drugs and a corresponding increase in the incidence of ADRs. Older patients demonstrate an exaggerated response to central nervous system-active drugs (eg, benzodiazepines, anesthetics, opioids) and a decreased response to some cardiovascular agents (eg, beta-adrenergic agents). Also, the most important pharmacokinetic changes in older people include a decrease in the excretory capacity of the kidney, rather than a decline in the rate of hepatic drug metabolism. The most frequent ADRs causing hospital
Predictors of and risk factors for ADR-related hospitalization in older patients

Despite concerns that ADRs represent an important medical problem in older patients, the predictive factors are still poorly understood, particularly in the community-dwelling elderly. The characteristics and major findings of studies that have investigated the risk factors for ADR-related hospital admission in older patients are shown in Table 3.

Age as a significant contributing factor to ADR-related hospitalization had been observed in community-dwelling older patients in some studies.\(^5,21,23\) The odds of experiencing severe ADRs increased by 3% per 1-year increase in age above 66 years.\(^21\)

The number of drugs being taken has also been highlighted in many studies as an independent risk factor for ADR-related hospital admissions.\(^5,12,17,21,23,24,35,38\) It has been estimated that the chance of an older patient having an ADR increases from 10%, when one medication is used, to 75% if more than five medications are used concurrently.\(^39\) The risk increase of an older patient (mean age 70 years) having an ADR-related hospitalization is 24% for each drug increase.\(^5\)

The prevalence of multimorbidity (the coexistence of multiple chronic diseases) in older patients ranges from 55% to 98% based on the systematic reviews.\(^40\) The presence of comorbidity also predicted ADR-related hospitalization in community-dwelling older patients.\(^3,19,21,36,41\) Relevant comorbidities included ischemic heart disease; heart failure; depression; diabetes; peripheral vascular disease; and pulmonary, rheumatological, hepatic, renal, and malignant diseases. In a population-based retrospective study, comorbidity predicted repeat admission for ADRs in older patients, especially those with comorbidities often managed in the community.\(^41\)

Potentially inappropriate drug prescribing is highly prevalent among community-dwelling older patients, and potentially inappropriate medications (PIMs) in these patients are significantly associated with ADRs and subsequent hospital admission.\(^42,43\) According to Price et al, exposure to a PIM from the Beers list of medications was associated with a significant increase in unplanned hospitalizations (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.15–1.21).\(^44\) There was also an increase in inpatient visits (OR 1.99, 95% CI 1.76–2.26) in older patients who were prescribed PIMs based on a retrospective cohort study.\(^45\)

A range of other factors has also been associated with ADR-related hospitalization, but these associations have

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**Table 1** Most common ADRs causing hospitalization in the elderly

<table>
<thead>
<tr>
<th>Most common ADRs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal complications(^5,18,23)(–24)</td>
<td>Gastrointestinal bleeding, peptic ulcer, erosive gastritis, nausea, vomiting</td>
</tr>
<tr>
<td>Cardiovascular disorders(^12,18,19,22)</td>
<td>Hypertension, bradycardia, falls, arrhythmias</td>
</tr>
<tr>
<td>Metabolic/endocrine complications(^5,12,22)(–24)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Renal and urinary disorders(^22)(–24)</td>
<td>Renal impairment, acute renal failure</td>
</tr>
<tr>
<td>Electrolyte disorders(^20,22)</td>
<td>Hypokalemia, hyperkalemia, hyponatremia</td>
</tr>
<tr>
<td>Nervous system disorders(^12,22)</td>
<td>Depressed level of consciousness, mental status changes</td>
</tr>
</tbody>
</table>

**Abbreviation:** ADRs, adverse drug reactions.

admission in older patients are typically gastrointestinal disorders\(^5,18,22\)\(–24\) and cardiovascular and metabolic/endocrine complications.\(^5,12,18,19,22\)\(–24\) A summary of the most common ADRs causing hospitalization in older patients is shown in Table 1.

**Drugs most frequently causing ADR-related hospitalization in older patients**

Older patients, due to the presence of multiple disease states, frequently use medications including prescription, over-the-counter, and herbal preparations. According to a survey conducted in 3,005 community-dwelling older adults aged 57–85 years in the USA, at least one prescription medication was used by 81% of the overall survey population and five or more prescription medications were used by 36% of people aged 75–85 years.\(^34\) The drugs most frequently causing ADR-related hospital admissions in older patients have varied between studies; these findings are summarized in Table 2.

**Table 2** Most common drugs causing ADR-related hospital admission in the elderly

| Antibacterials\(^5,18,23\) |                                                                                     |
| Anticonvulsants\(^58\) |                                                                                     |
| Antineoplastic agents\(^1,35\) |                                                                                     |
| Antipsychotics\(^1,35\) |                                                                                     |
| Antithrombotics (anticoagulants and antiplatelets)\(^18,20,23,24,35,58\) |                                                                                     |
| Cardiovascular drugs (diuretics,\(^18,20,23,24,35\) cardiac glycosides,\(^1,18,35\) angiotensin-converting enzyme inhibitors,\(^5,12,24,35,58\) beta-blockers,\(^29,58\) antiarrhythmics,\(^18,24\) calcium channel blockers\(^1\)) |                                                                                     |
| Corticosteroids\(^3\) |                                                                                     |
| Hypoglycemics\(^3,58\) |                                                                                     |
| Nonsteroidal anti-inflammatory drugs\(^5,18,22,24,35,58\) |                                                                                     |

**Abbreviation:** ADR, adverse drug reaction.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year conducted</th>
<th>Design</th>
<th>Duration</th>
<th>Settings</th>
<th>Mean/median age (years)</th>
<th>Main outcome measures</th>
<th>Predictors/risk factors</th>
</tr>
</thead>
</table>
| Onder et al⁵ | Italy | 1988–1997 | Multicenter pharmacoepidemiology survey | 10 years | Academic hospitals | 70 | ADR severity, potentially responsible drugs, predictors | Female sex (OR 1.30, 95% CI 1.10–1.54)  
Alcohol use (OR 1.39, 95% CI 1.20–1.60)  
Number of drugs (OR 1.24, 95% CI 1.20–1.27 for each drug increase)  
Severe ADRs  
Age (OR 1.50, 95% CI 1.01–2.23 for age 65–79 years and OR 1.53, 95% CI 1.00–2.33 for age ≥80 years)  
Comorbidity (OR 1.12, 95% CI 1.05–1.20 for each point in the CCI)  
Number of drugs (OR 1.18, 95% CI 1.11–1.25 for each drug increase) |
| Marcum et al¹² | USA | 2004–2006 | Retrospective cohort | 3 years | All admissions (veterans) | 76.4 | ADR causality, preventability, predictors | Polypharmacy (≥9 and 5–8 medications)  
AOR 3.90, 95% CI 1.43–10.61 and AOR 2.85, 95% CI 1.0–7.85, respectively |
| Mannesse et al¹⁷ | The Netherlands | 1994 | Observational cross-sectional | 3 months | University hospital | 78 | Risk indicators for severe ADRs | Fall before admission (OR 5.13, P=0.006)  
Gastrointestinal bleeding or hematuria (OR 19.8, P<0.001)  
Use of three or more drugs (OR 9.8, P=0.04) |
| Franceschi et al⁹ | Italy | 2004–2005 | Prospective cross-sectional | 1 year | Geriatric | 76.5 | ADR prevalence, avoidability | Drug–drug interactions (32.3%)  
Inappropriate prescription (21.8%)  
Ischemic heart disease (OR 4.50, 95% CI 1.36–14.88)  
Depression (OR 2.49, 95% CI 1.08–5.77)  
Heart failure (OR 2.08, 95% CI 1.13–3.81) |
| Wawruch et al¹⁹ | Slovakia | 2003–2005 | Retrospective cross-sectional | 1.4 years | Internal medicine | 76.6 | ADR predictors | Sex (for females, AOR 0.81, 95% CI 0.72–0.92)  
Age (OR 1.03, 95% CI 1.02–1.04)  
CCI score ≥3 (AOR 1.86, 95% CI 1.48–2.33)  
Number of drugs (AOR 1.48, 95% CI 1.13–1.93 for 6–10 drugs and AOR 1.93, 95% CI 1.49–2.51 for ≥11 drugs)  
Multiple pharmacies (AOR 1.13, 95% CI 1.00–1.27)  
Newly prescribed drugs (AOR 1.17, 95% CI 0.93–1.47)  
Recent hospital admission (AOR 1.47, 95% CI 1.23–1.76)  
Long-term care residence (AOR 2.08, 95% CI 1.62–2.67)  
Age ≥65 years (OR 1.59, 95% CI 1.10–2.29)  
Number of drugs taken 3–5 (AOR 2.5, 95% CI 1.2–5.1)  
Number of drugs taken 6–9 (AOR 2.8, 95% CI 1.4–5.4)  
Number of drugs taken 10 (AOR 4.0, 95% CI 1.7–9.3) |
| Wu et al²¹ | Canada | 2003–2008 | Retrospective cohort | 5 years | Emergency department | 77 | Incidence, cost, risk factors | Sex (for females, AOR 0.81, 95% CI 0.72–0.92)  
Age (OR 1.03, 95% CI 1.02–1.04)  
CCI score ≥3 (AOR 1.86, 95% CI 1.48–2.33)  
Number of drugs (AOR 1.48, 95% CI 1.13–1.93 for 6–10 drugs and AOR 1.93, 95% CI 1.49–2.51 for ≥11 drugs)  
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Number of drugs taken 6–9 (AOR 2.8, 95% CI 1.4–5.4)  
Number of drugs taken 10 (AOR 4.0, 95% CI 1.7–9.3) |
| Pedros et al²³ | Spain | 2009–2010 | Cross-sectional | 120 days | Teaching hospital | 75 | ADR predictors | Age $≥65$ years (OR 1.59, 95% CI 1.10–2.29)  
Number of drugs taken 3–5 (OR 5.07, 95% CI 2.71–9.50), 6–9 (OR 5.90, 95% CI 3.16–11.01), and ≥10 (OR 8.94, 95% CI 4.73–16.89)  
Number of drugs (OR 1.06, 95% CI 1.01–1.10) |
| Alexopoulou et al²⁴ | Greece | 2005 | Prospective cross-sectional | 6 months | University hospital | 65 | Frequency of ADRs, causality, severity, preventability, predictors | Number of drugs (OR 1.18, 95% CI 1.08–1.29)  
Self-medication (OR 2.34, 95% CI 1.18–4.66)  
Use of antithrombotics (OR 2.26, 95% CI 1.33–3.88)  
Use of antibacterial drugs (OR 4.04, 95% CI 1.50–10.83) |
| Olivier et al²⁵ | France | 2002–2003 | Prospective cross-sectional | 4 weeks | Emergency department | 80.2 | ADR incidence, risk factors | Number of drugs (OR 1.18, 95% CI 1.08–1.29)  
Self-medication (OR 2.34, 95% CI 1.18–4.66)  
Use of antithrombotics (OR 2.26, 95% CI 1.33–3.88)  
Use of antibacterial drugs (OR 4.04, 95% CI 1.50–10.83) |
The need for an ADR prediction tool in older patients in primary care

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Time Period</th>
<th>Setting</th>
<th>Duration</th>
<th>ADR predictors</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malhotra et al.</td>
<td>India</td>
<td>Prospective cross-sectional</td>
<td>2000</td>
<td>Emergency department</td>
<td>7 months</td>
<td>Number of drugs ≥3 (OR 4.3) Consulting ≥3 physicians (OR 5.7) Living alone (OR 4.3) Number of drugs (AOR 4.1, 95% CI 2.4–6.9 for 3–7 drugs; AOR 6.4, 95% CI 3.7–11.0 for eight or more drugs) and increased concentration of serum creatinine (AOR 1.5, 95% CI 1.1–2.2) Sex (HR 1.08, 95% CI 1.02–1.15, for men) First admission in 1995–1999 (HR 2.34, 95% CI 2.00–2.73) Length of hospital stay (HR 1.11, 95% CI 1.05–1.18, for stays ≥14 days) CCI (HR 1.71, 95% CI 1.46–1.99, for score ≥7) Comorbid congestive cardiac failure (HR 1.56, 95% CI 1.43–1.71), peripheral vascular disease (HR 1.27, 95% CI 1.09–1.48), chronic pulmonary disease (HR 1.61, 95% CI 1.45–1.79), rheumatological disease (HR 1.65, 95% CI 1.41–1.92), mild liver disease (HR 1.48, 95% CI 1.05–2.07), moderate to severe liver disease (HR 1.85, 95% CI 1.18–2.92), moderate diabetes (HR 1.18, 95% CI 1.07–1.30), diabetes with chronic complications (HR 1.91, 95% CI 1.65–2.22), renal disease (HR 1.93, 95% CI 1.71–2.17), any malignancy including lymphoma and leukemia (HR 1.87, 95% CI 1.68–2.09), and metastatic solid tumors (HR 2.25, 95% CI 1.92–2.64)</td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>Taiwan</td>
<td>Prospective case-control</td>
<td>2009–2010</td>
<td>Emergency department</td>
<td>1 year</td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>Australia</td>
<td>Retrospective cohort</td>
<td>2005</td>
<td>Records of ADR admission from 1980 to 2000 and followed for 3 years</td>
<td>Mean age not reported, ADR predictors reported, study in patients aged ≥60 years</td>
<td>Risk factors</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reaction; OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; AOR, adjusted odds ratio; HR, hazard ratio.

In older patients due to adverse drug reactions, the presence of drug interactions was identified as a risk factor for ADRs in one study. Female sex was also associated with ADR-related hospitalization in older patients. The need for an ADR prediction tool has emerged in recent years, which aims to assist health care professionals in their decision making regarding the stratification of individuals or group of individuals by absolute risk that a certain outcome is present and enable them to pay extra attention to a patient’s medications when they experience a certain outcome. Risk prediction models have begun to emerge in recent years, which use multiple predictors to estimate the absolute risk that a certain outcome is present and enable health care professionals in their decision making regarding further management and to inform individuals about their risk of developing a medical problem. These tools are particularly useful in individual risk assessment, and they are usually developed to guide health care professionals in their decision making regarding further management and to inform individuals about their risk of developing a medical problem.
The GerontoNet ADR risk score is one such validated model proposed by Onder et al to identify hospitalized patients who are at an increased risk of an ADR. This risk score identified several risk factors for the development of ADRs and developed a score that allows stratification of patients according to the likelihood of an ADR. The strongest predictors of ADRs in this study were the number of medications and a history of an ADR, followed by the presence of heart failure, liver disease, four or more medical conditions, and renal failure. The GerontoNet ADR risk score was reported to have satisfactory predictive value for ADRs with an area under the curve (AUC) of 0.71 (95% CI 0.68–0.73).

But, one of the important limitations of this study was that data on the preventability of ADRs were not collected, so the authors could not assess the risk factors for preventable ADRs. Also, these study findings cannot be extrapolated to older patients living in the community setting since the data were collected based on hospitalized patients 65 years or above. Another important limitation is that the GerontoNet ADR risk score did not account for the use of PIMs as a risk factor, which could be a stronger predictor of ADRs.

O’Connor et al investigated the clinical applicability and the ability to predict ADRs using the GerontoNet ADR risk score in hospitalized older patients. The variables that increased ADR risk in their alternative model included renal failure, increasing number of medications, inappropriate medications, and age $\geq$ 75 years. The study results showed more research has been focused on ADRs occurring in the hospital than in the community setting.

The contemporary validated ADR risk prediction tools used in hospital settings, detailed in Table 5, could be used as guides to develop similar models in community settings.

### Table 4 An overview of predictors of ADR-related hospital admission in the elderly

<table>
<thead>
<tr>
<th>Frequently reported predictors</th>
<th>Other predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medications $^{5,12,17,21,23,25-38}$</td>
<td>Drug interactions $^{18}$</td>
</tr>
<tr>
<td>Comorbid conditions $^{5,19,21,36,41}$</td>
<td>Female sex $^{5}$</td>
</tr>
<tr>
<td>Age $^{5,12,21}$</td>
<td>Self-medication $^{25}$</td>
</tr>
<tr>
<td>Potentially inappropriate medications $^{54,45}$</td>
<td>Use of antithrombotics $^{25}$</td>
</tr>
<tr>
<td></td>
<td>Use of antibacterial drugs $^{35}$</td>
</tr>
<tr>
<td></td>
<td>Alcohol use $^{5}$</td>
</tr>
<tr>
<td></td>
<td>Falls before admission $^{17}$</td>
</tr>
<tr>
<td></td>
<td>Patients living alone $^{37}$</td>
</tr>
<tr>
<td></td>
<td>Increased serum creatinine $^{38}$</td>
</tr>
<tr>
<td></td>
<td>Multiple pharmacy visits $^{21}$</td>
</tr>
<tr>
<td></td>
<td>More than three consulting physicians $^{27}$</td>
</tr>
<tr>
<td></td>
<td>Newly prescribed drugs $^{31}$</td>
</tr>
<tr>
<td></td>
<td>Recent hospital admission $^{21}$</td>
</tr>
<tr>
<td></td>
<td>Long-term care residence $^{32}$</td>
</tr>
<tr>
<td></td>
<td>Patients with diabetes or neoplasms $^{27}$</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal bleeding or hematuria $^{17}$</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease $^{19}$</td>
</tr>
<tr>
<td></td>
<td>Depression $^{19}$</td>
</tr>
<tr>
<td></td>
<td>Heart failure $^{19}$</td>
</tr>
</tbody>
</table>

### Table 5 Features of validated ADR prediction tools for elderly hospitalized patients

<table>
<thead>
<tr>
<th>Features</th>
<th>Onder et al $^{49}$ (GerontoNet ADR risk score)</th>
<th>Tangiisuran et al $^{48}$ (BADRI) model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Retrospective cohort</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Developmental stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validation stage</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Main outcome measure</td>
<td>ADR (6.5%)</td>
<td>ADR (12.5%)</td>
</tr>
<tr>
<td>Age of study participants (years)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>78 (7.2)</td>
<td>85 (81–89)</td>
<td></td>
</tr>
<tr>
<td>Most common ADRs</td>
<td>Cardiovascular and arrhythmic complications</td>
<td>$\geq$ 8 drugs</td>
</tr>
<tr>
<td>$\geq$ 4 Comorbid conditions</td>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td>Raised white cell count</td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
<td>Use of antidiabetic agents</td>
</tr>
<tr>
<td>Number of drugs</td>
<td></td>
<td>Length of stay $\geq 12$ days</td>
</tr>
<tr>
<td>History of ADR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviation: ADR, adverse drug reaction.

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that 37.7% of ADRs were not predicted by the GerontoNet ADR risk score. The authors’ model included additional predictors like PIMs which would influence the presence of ADRs, but had a lower predictive value for ADRs (AUC of 0.62 [95% CI 0.57–0.68]) compared to the GerontoNet ADR risk score.

Tangisuran et al recently developed and validated an ADR risk model in a population of patients with a median age of 85 years.48 This model was based on five clinical variables, some of which have not been previously reported. Compared with the GerontoNet ADR risk score and the model developed by O’Connor et al, this model had a higher predictive value for ADRs. Again, this model did not account for the use of PIMs as a risk factor. Also, this model did not use a uniform criterion for causality assessment of ADRs, which might have affected the outcome of the study.

The utility of an ADE trigger tool had been explored in a few studies conducted among older patients living in the community. One such tool used a 39-item trigger tool in patients aged 65 years or above in ambulatory primary care practices.56 The most common triggers and their positive predictive values (PPVs) for ADE were “Medication stop” (26.3%), “Hospitalization” (21.8%), and “Emergency Room visit” (14.9%). Most of the triggers had very low PPVs and only nine of the triggers had PPVs >5% which could detect 94.4% of the ADEs. Similarly, the utility of an ADE trigger tool in Veterans Affairs nursing homes has also been studied and found an overall PPV of 40.1%.57 The most common ADEs detected by this tool were acute kidney injury, hypokalemia, hypoglycemia, and hyperkalemia. Even though these tools could be used to identify ADEs in community-dwelling older patients, there is a clear need to predict the future occurrence of these events, especially ADRs.

Development of an ADR prediction tool for older patients in primary care
A study has suggested that the majority of older patients had their own family physicians (95%) at the time of presenting to the emergency department due to ADRs.21 Primary care physicians are best able to understand the complete medical, functional, and social issues that are in play when optimizing medications in older people living in the community. Since the older population is likely to have multiple risk factors for ADRs, ideally, the GPs should be able to predict those older adults who have a severe risk of ADRs that may lead to emergency hospital admissions. The development of an ADR prediction tool in community settings would facilitate this. The design of such a tool would require identification of a comprehensive list of possible predictive factors contributing to ADR-related hospitalization based on the literature, available validated ADR prediction tools, and clinical experience. These predictive factors could then be quantified in large populations of elderly subjects admitted and not admitted to hospital with an ADR preferably using a prospective study design. Univariate and multivariate analyses could be undertaken and the significant predictors of ADR-related hospitalization assigned a score based on their respective ORs. Finally, an ADR risk score could be computed based on the sum of the scores of individual variables as described by Onder et al, with a subsequent validation stage.49 A risk score may also be used to improve prescribing practice. The ADR risk score could potentially be integrated into prescribing software to alert GPs regarding their patients’ risk of ADRs and prompt appropriate preventive measures, which might include medication review in high-risk patients, avoiding inappropriate medications, comprehensive geriatric assessment,4 and cessation of high-risk medications which are least likely to be beneficial. Similarly, policy makers could use the score to target limited health care resources to patients in real need of intervention to address the issue of quality use of medicines.

Conclusion
It is clear that older patients are at significant risk of hospital admissions due to ADRs and many ADRs occurring in this population are considered preventable. There is a need for greater understanding of the predictors of ADRs in these patients, and how these predictors are interrelated. This will provide the basis for improved risk assessment practices. Even though various risk models in older populations have been suggested for use in hospital settings, there is a clear need for a simple, practical, and efficient tool to identify the high-risk group of older patients most likely to be admitted to hospital due to ADRs. These patients can be targeted in order to reduce their risk of ADRs and their associated morbidity and costs.

Disclosure
The authors report no conflicts of interest in this work.

References


