Adverse drug reactions in older patients during hospitalisation: are they predictable?

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Abstract

Background: adverse drug reactions (ADRs) are a major cause of morbidity and healthcare utilisation in older people. The GerontoNet ADR risk score aims to identify older people at risk of ADRs during hospitalisation. We aimed to assess the clinical applicability of this score and identify other variables that predict ADRs in hospitalised older people.

Methods: we prospectively studied 513 acutely ill patients aged ≥65 years. The GerontoNet ADR risk score was calculated for all patients. ADRs were identified through patient and physician consultation together with analysis of case notes. Receiver operator characteristic (ROC) curves were constructed to test the ability of the GerontoNet risk score to predict ADRs. Multivariate logistic regression examined the influence of individual variables on the presence of ADRs.

Results: in-hospital ADRs were identified in 135 patients (26%). The area under the ROC curve was 0.62 (95% CI: 0.57–0.68). Variables which increased ADR risk include (i) renal failure (OR: 1.81, 95% CI: 1.12–2.92), (ii) increasing number of medications (OR: 1.09, 95% CI: 1.02–1.17) (iii) inappropriate medications (OR: 2.40, 95% CI: 1.26–4.50) and (iv) age ≥75 years (OR: 2.12, 95% CI: 1.23–3.70).

Conclusion: the GerontoNet ADR risk score incorrectly classified 38% of patients as low risk. Inappropriate medications and increasing age also contribute to ADR risk.

Keywords: adverse drug reactions, elderly, hospitalisation, risk factors, GerontoNet ADR risk score, elderly

Introduction

Preventing avoidable harm to patients is a key focus of healthcare provision [1, 2], one such example being adverse drug reactions (ADRs) which are defined as any noxious, unintended and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning and drug abuse [3]. ADRs are common with prevalence rates of 6.5% in the community [4] rising to 31% in hospital [5]; older adults are more at risk because of increased drug consumption, and age-related changes in pharmacokinetics and pharmacodynamics [6]. Indeed older adults are seven times more likely to have an ADR requiring hospitalisation than younger persons [7] and while in hospital acutely ill older patients with multiple concurrent chronic illness are significantly more susceptible to ADRs than younger patients [8–10]. Inappropriate prescribing (IP) of medicines is also a major risk factor for ADRs in older patients [11–13]; a recent study reporting an 83% increased risk of ADRs [14] in older patients receiving a potentially inappropriate medication (PIM) as defined by STOPP (Screening Tool of Older Persons’ Prescriptions) [15].

ADRs have important clinical and economic consequences. Firstly, ADRs are a leading cause of hospitalisation in older patients, with recent studies showing that 11.5–14% of older patients had an ADR that was causal or contributory to admission [14, 16]. Secondly, ADRs are costly to treat; the Institute of Medicine in the USA estimated the annual cost of treating ADRs at $3.5 billion [17]. Thirdly, ADRs are associated with increased mortality; fatal ADRs account for 3% [18] of all deaths in the general population rising to 5% [19] in hospitalised
patients. The majority of ADRs (70%) are thought to be avoidable [4, 14]. By preventing ADRs there is great potential to improve clinical outcomes and reduce health expenditure.

The GerontoNet ADR risk score [8] was recently developed by the Italian Group of Pharmacoepidemiology in the Elderly as a means of stratifying older patients into groups at varying risk of ADRs. The tool comprises six variables; (i) at least four co-morbidities, (ii) >5 medications, (iii) renal failure, (iv) heart failure, (v) liver disease and (vi) previous ADR. Each variable has a score that reflects the odds of an ADR occurring (Table 1). The GerontoNet risk score [8] 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) [8]. However, this implies that 29% were incorrectly stratified into a lower risk category. For any ADR risk score to become widely adopted into clinical practice, it must be reliable, valid and reproducible in a various clinical settings.

We aimed to examine the GerontoNet ADR risk score in terms of its clinical applicability, and its ability to predict ADRs in hospitalised older patients when compared with expert judgement. We also aimed to identify other variables which would influence the presence of ADRs in this group.

Methods

Study setting and population

The study was conducted in an 810 bed university teaching hospital in Ireland. Using an estimated prevalence of ADRs of 25% [14] a precision of 4 and 95% level of confidence, a minimum sample size of 450 patients was required. Consecutive emergency admissions of patients aged ≥65 years were prospectively studied from July 2010 to October 2010. Patients admitted to the general medical and surgical services were included; those admitted to the Intensive Care Unit, psychiatry or palliative care services were excluded. The local Clinical Research Ethics Committee approved the study. All patients provided informed consent.

Data collection

Standard baseline demographics, current diagnoses, concurrent medications and baseline laboratory and electrocardiographic data were recorded by the primary researcher (M.O.C.) who is clinically trained in geriatric medicine and experienced in geriatric pharmacotherapy. Co-morbidity was quantified using the modified cumulative illness rating scale (mCIRS) [20]. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) formula. [21]. Cognitive impairment was defined as a diagnosis of dementia or cognitive impairment as documented in the case notes. Functional independence was measured using the Barthel index [22]. PIMs were identified by STOPP criteria [15, 16]. Patients were subsequently reviewed on Day 5 of admission and, where applicable, on Day 10 when medications, laboratory parameters and other relevant clinical investigations were updated.

The GerontoNet ADR risk score [8] was calculated for all patients on admission, Day 5 and Day 10 (where applicable), but modification to some of the variables was required to ensure consistent application in all patients. These included (i) ‘heart failure’ which was defined according to the New York Heart Association (NYHA) classification; patients scored ‘0’ with NYHA I and II and ‘1’ with NYHA III or IV symptoms; (ii) ‘liver disease’ which was defined as synthetic liver dysfunction, or liver injury with raised transaminases greater than twice the normal range or documented liver disease and (iii) ‘number of medications’ with patients scoring ‘0’ for zero to five drugs and ‘1’ for six to seven drugs (Table 1).

ADRs were identified on Day 5 and Day 10 of admission by the primary researcher. This comprised a multifaceted approach including patient and physician consultation, detailed review of medical and nursing records, and detailed assessment of laboratory, radiological and other relevant clinical investigations. An ADR was suspected if the patient’s symptoms/signs or laboratory abnormalities were (i) consistent with the known adverse effect profile of the drug (using the British National Formulary Edition 59, March 2010), (ii) if there was a clear temporal relationship with the start of the drug and (iii) if, after appropriate investigations, other causes of symptoms were excluded. All ADRs were discussed with a consultant geriatrician (D.O.M.) and agreement by both M.O.C. and D.O.M. was required to confirm an ADR. ADR causality was defined using The World Health Organization Uppsala Monitoring Committee (WHO—UMC) causality criteria [23]; only ADRs classified as certain and probable were included in the analysis. An ADR was defined as severe if (i) it caused death or disability, (ii) resulted in admission to an intensive care unit or (iii) required administration of an antidote.

Table 1. GerontoNet ADR risk score [8].

<table>
<thead>
<tr>
<th>GerontoNet ADR risk score as applied by Onder et al. [8]</th>
<th>Points</th>
<th>GerontoNet ADR risk score as applied in this study</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4 co-morbid conditions</td>
<td>1</td>
<td>≥ 4 co-morbid conditions</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>Heart failurea</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1</td>
<td>Liver diseaseb</td>
<td>1</td>
</tr>
<tr>
<td>Number of drugs</td>
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<td>Number of drugs</td>
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<tr>
<td>≤ 5</td>
<td>0</td>
<td>≤ 5</td>
<td>0</td>
</tr>
<tr>
<td>5–7</td>
<td>1</td>
<td>6–7</td>
<td>1</td>
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<tr>
<td>≥ 8</td>
<td>4</td>
<td>≥ 8</td>
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<tr>
<td>Previous ADR</td>
<td>2</td>
<td>Previous ADR</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>Renal failure</td>
<td>1</td>
</tr>
</tbody>
</table>

ADR, adverse drug reaction.
aNew York Heart Association Class III or IV.
bLiver disease documented in medical notes/synthetic liver disease/transaminases greater than twice normal limit.

eEstimated glomerular filtration rate ≤60 ml/min/1.73 m².
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Statistical analysis

The statistical analysis was performed using PASW version 18 for Windows (SPSS™, Inc., Chicago IL, USA). Descriptive statistics included median and inter-quartile range (IQR) for non-parametric data and mean and standard deviation for normally distributed data. The Chi-squared ($\chi^2$) test was used for baseline comparisons between those who had an ADR and those who did not. The Mann–Whitney $U$ test was used to determine the independence of non-parametric variables. Variables identified as being significantly associated with ADRs (i.e. $P < 0.05$) on univariate analysis were entered into a multiple logistic regression model to examine the influences of such variables on the presence of an ADR. Age, renal failure, liver disease and functional dependence were entered as categorical variables; number of medications and number of PIMs were entered as continuous variables using a block entry procedure; results are presented as odds ratios (OR) with 95% confidence intervals. Receiver operator characteristic (ROC) curves were constructed and the AUC calculated to determine the predictive ability of the GerontoNet ADR risk score in correctly classifying ADRs.

Results

Patient characteristics

Data were collected from 513 patients; the median (IQR) age was 77 (72–82) years, 56% patients were female. Sixty-one patients (12%) were nursing home residents, the remainder were community dwelling. Two hundred forty-three patients (47%) required assistance for at least one ADL according to the Barthel index [22]. Eighty per cent of patients ($n = 412$) had at least four chronic co-morbidities. Two hundred twenty-two patients (48%) had an eGFR $\leq 60$ ml/min/1.73 m$^2$, 65 (13%) had heart failure NYHA class III or IV. Eighty-seven patients (17%) had a diagnosis of dementia. The median (IQR) mCIRS [20] on admission was 22 (19–25). The median (IQR) number of prescribed medications was 7 (1–10); the total number of prescribed medications was 3,818. Thirty-three per cent ($n = 168$) were prescribed at most five medications; 46% were prescribed between 6 and 10 medications, 21% were prescribed $\geq 11$ medications. Two hundred sixty-two patients (12%) were nursing home residents, the remainder were community dwelling. Two hundred sixty-two patients (12%) were nursing home residents, the remainder were community dwelling. Two hundred sixty-two patients (12%) were nursing home residents, the remainder were community dwelling.

Univariate analysis variable | ADR ($n = 135$) | No ADR ($n = 378$) | $P$-value
---|---|---|---
Age (years) | | |
Median (IQR) | 79 | 75 | $<0.001$
65–74 (%) | 34 (25) | 153 (40.5) |
75–84 (%) | 67 (50) | 153 (40.5) | 0.006
$\geq 85$ (%) | 34 (25) | 72 (19) |
Renal failure (%) | 73 (54) | 149 (39) | 0.003
Liver disease (%) | 16 (11.8) | 21 (5.5) | 0.015
Heart failure (%) | 19 (4) | 46 (12) | 0.568
Dementia (%) | 22 (16.3) | 65 (17) | 0.811
At least four co-morbidities (%) | 115 (85) | 301 (79.6) | 0.157
Inappropriate prescription/STOPP medications (%) | 81 (60) | 179 (47.3) | 0.012
At least 1 activity of daily living (%) | 44 (32.6) | 72 (19) | 0.001
Multivariate analysis variable (%) | Odds ratio $95\%$ confidence interval $P$-value
---|---|---|---|---
Age (years) | | | |
65–74 | 2.12 | 1.22 | 3.69 | 0.007
75–84 | 2.22 | 1.68 | 4.23 | 0.015
$\geq 85$ | 1.81 | 1.12 | 2.92 | 0.015
Renal failure | 1.86 | 0.90 | 3.84 | 0.90
Liver disease | 2.40 | 1.26 | 4.59 | 0.008
Number of STOPP medications | 1.09 | 1.02 | 1.17 | 0.006
Number of medications | 0.75 | 0.45 | 1.26 | 0.290

Adverse drug reactions

One hundred and seventy-eight ADRs were identified in 135 patients, an ADR incidence rate of 26%. WHO–UMC causality criteria [24] categorised 29% of ADRs as certain, 66% as probable and 5% as possible. Twenty-four per cent of ADRs were severe. The most common ADRs were acute kidney injury and electrolyte disturbance secondary to diuretics ($n = 45$), falls secondary to (i) benzodiazepines ($n = 32$) and (ii) opiates ($n = 32$), orthostatic hypotension/symptomatic bradycardia secondary to anti-hypertensives ($n = 30$) and upper gastrointestinal bleeding, gastritis and acute kidney injury secondary to non-steroidal anti-inflammatories ($n = 10$). (Supplementary data are available in Age and Ageing online, Appendix SI).

Patients with ADRs were compared with those without ADRs (Table 2). Those with ADRs were significantly older (79 versus 75 years, $Z = 3.651$, $P < 0.001$), were more likely to have renal impairment ($\chi^2 = 8.704$; $P < 0.005$), were more dependent with ADLs ($\chi^2 = 10.429$; $P < 0.001$), were prescribed more medications (median number of daily medications 10 versus 7, $P < 0.001$) and received more PIMs ($\chi^2 = 6.36$; $P = 0.012$). There were no differences between these groups in terms of gender, burden of comorbidity and prevalence of dementia. Patients with ADRs...
also had a longer hospital stay (median: 12 days) compared with those without ADRs (median: 7 days; \( P < 0.001 \)). Variables identified as being significantly associated with ADRs on univariate analysis were entered into a multiple logistic regression model to examine their influence on the development of an ADR. These results are presented in Table 2. In brief age \( \geq 85 \) years compared with age 65–74 years (OR: 2.22, 95% CI: 1.68–4.23, \( P = 0.015 \)), eGFR \( \leq 60 \) ml/min/1.73 m\(^2\) (OR: 1.81, 95% CI: 1.12–2.92, \( P = 0.015 \)), increasing number of medications (OR: 1.09, 95% CI: 1.02–1.17, \( P = 0.006 \)) and IP (OR: 2.40, 95% CI: 1.25–4.50, \( P = 0.008 \)) were significantly and independently associated with having an ADR (Table 2).

**GerontoNet ADR risk score**

Fifty per cent of the study population scored \( \geq 4 \) on admission, with eGFR \( \leq 60 \) ml and increasing number of medications the most significant contributory variables to the score. A quarter (25%) of all patients had a higher GerontoNet ADR risk score [8] on discharge than on admission to hospital. This was a consequence of increased number of medications at discharge compared with admission. The median (IQR) GerontoNet risk score in those who had an ADR was 5 (2–6) and 3 (1–6) in those without an ADR. To evaluate the diagnostic accuracy of the GerontoNet ADR risk score in predicting ADRs, ROCs using the calculated ADR risk scores yielded AUC values of: (0.62, 95% CI: 0.57–0.68) on admission, 0.51 (95% CI: 0.46–0.57) on Day 5 and 0.55 (95% CI: 0.47–0.62) on Day 10 (Figure 1).

**Discussion**

The principal findings of this study are (i) 26% of older patients had an ADR following admission to hospital, (ii) the principal risk factors for ADRs were increasing age, renal impairment, increasing number of medications and use of potentially inappropriate medicines and (iii) the GerontoNet ADR risk score did not reliably predict ADRs in almost 40% of cases.

Our ADR rate of 26% is comparable with other studies [8, 24, 25] emphasising the high prevalence of ADRs. Although many of the risk factors for ADRs are often irreversible, e.g. renal impairment, burden of co-morbidity, and liver disease; polypharmacy is one risk factor that can be addressed by all clinicians. Our study showed that increasing number of medications is an independent risk factor for ADRs (OR: 1.09, 95% CI: 1.02–1.17, \( P = 0.006 \)), i.e. with each additional prescribed medication the risk of an

![Figure 1](image-url). ROC curve of GerontoNet ADR risk score and ADRs (i) on admission (ii) on Day 5 and (iii) Day 10.
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ADR increases by 9%. It is well established that increasing number of medications is also associated with IP [9, 16], another potentially reversible risk factor. In this study, each additional PIM was associated with a twofold increased risk of an ADR (OR: 2.40, 95% CI: 1.26-4.59). Clearly, measures of IP should be included in future ADR risk scores. A recent randomised controlled trial (RCT) demonstrated that screening for IP on admission led to sustained and significant reductions in drug–drug and drug–disease interactions in older hospitalised patients [26], two of the main contributors to ADRs. Whether prospective application of IP screening tools, e.g. STOPP on admission to hospital can reduce the incidence of in-hospital ADRs in older people is the subject of a current RCT (NCT01467050).

Other variables identified in this study as being strongly predictive of in-hospital ADRs were age ≥85 years (OR: 2.22, 95% CI: 1.68–4.23) and renal failure (OR: 1.81, 95% CI: 1.12–2.92). Patients aged ≥85 years with renal failure were four times more likely to have an ADR than younger patients with normal renal function. Older patients with renal failure and IP were nine times more likely to have an ADR than patients without these risk factors. Though age cannot be modified and renal failure is often irreversible in older patients, prescribers should be cognisant of the fact that the oldest old and those with renal impairment are at greatest risk of an ADR, a tenet that should guide therapeutic decisions, particularly with respect to drug dosing and monitoring.

Results from our study show that the GerontoNet score will be higher 62.3% of times in those with an ADR compared with those without an ADR, i.e. 37.7% of ADRs are not predicted by the GerontoNet ADR risk score. For the GerontoNet ADR risk score to have high discriminating value, the ROC curve should yield AUC values close to 1.0, the ideal number for the predictive value when the false positive rate is graphically plotted against the true positive rate. In the ROC curves illustrated in Figure 1, the AUC values that discriminate ADR cases from non-ADR cases fall well below 1.0. Potential explanations as to why our results differ from those in the original GerontoNet ADR risk score study may lie in the interpretation of the variables within the score. Reproducibility of any scoring tool relies on clearly defined variables. In the original description of the GerontoNet risk score, definitions of heart failure and liver disease were not provided and thus are open to interpretation. In addition, the score for patients taking five medications is ambiguous, as it is included twice, i.e. at most five medications = 0 points and five to seven medications = 1 point (Table 1). Consequently, calculation of the risk score in individual patients has the potential to vary across different centres. This fundamentally affects the validity of the GerontoNet score in its current format.

Tangible outcomes such as reduction in ADR incidence and reduced healthcare utilisation costs should be the focus of future research. The GerontoNet ADR risk score in its current format is unlikely to reduce ADR incidence in hospitalised older people as in the present study as it misses almost 40% of those at risk. Recognition of risk factors such as inappropriate medication and increasing age in addition to renal failure and polypharmacy should be considered when prescribing for older people in order to reduce ADR risk. We propose that all of these variables should be incorporated into future ADR risk assessment tools.

**Key points**

- One in four older people had an ADR following admission to hospital.
- Diuretics, benzodiazepines and opiates accounted for >50% of the ADRs recorded.
- Risk factors for ADRs include polypharmacy, renal impairment, IP and age >75 years.

**Conflicts of interest**

None declared.

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**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

**References**

Childhood milk consumption is associated with better physical performance in old age

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