Enhanced clinical pharmacy service targeting tools: risk-predictive algorithms

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Keywords
age-adjusted co-morbidity, clinical pharmacy targeting, optimize patient outcomes, RAMI, readmission, risk-predictive algorithms

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Accepted for publication: 17 September 2014

doi:10.1111/jep.12276

Abstract

Rationale, aims and objectives This study aimed to determine the value of using a mix of clinical pharmacy data and routine hospital admission spell data in the development of predictive algorithms. Exploration of risk factors in hospitalized patients, together with the targeting strategies devised, will enable the prioritization of clinical pharmacy services to optimize patient outcomes.
Methods Predictive algorithms were developed using a number of detailed steps using a 75% sample of integrated medicines management (IMM) patients, and validated using the remaining 25%. IMM patients receive targeted clinical pharmacy input throughout their hospital stay. The algorithms were applied to the validation sample, and predicted risk probability was generated for each patient from the coefficients. Risk threshold for the algorithms were determined by identifying the cut-off points of risk scores at which the algorithm would have the highest discriminative performance. Clinical pharmacy staffing levels were obtained from the pharmacy department staffing database.
Results Numbers of previous emergency admissions and admission medicines together with age-adjusted co-morbidity and diuretic receipt formed a 12-month post-discharge and/or readmission risk algorithm. Age-adjusted co-morbidity proved to be the best index to predict mortality. Increased numbers of clinical pharmacy staff at ward level was correlated with a reduction in risk-adjusted mortality index (RAMI).
Conclusions Algorithms created were valid in predicting risk of in-hospital and post-discharge mortality and risk of hospital readmission 3, 6 and 12 months post-discharge. The provision of ward-based clinical pharmacy services is a key component to reducing RAMI and enabling the full benefits of pharmacy input to patient care to be realized.

Introduction

The concept of integrated medicines management (IMM) was proposed and designed by researchers in Northern Ireland, in response to key strategy reports within the United Kingdom [1–4]. The programme aimed to deliver health care benefits from timely and comprehensive integrated pharmacy services.

To date the programme has resulted in promising positive outcomes that reinforce the importance of the provision of coordinated clinical pharmacy services within the hospital setting. Many factors have played a role in the need to create an effective medicines management service, for example, an increase in the complexity of medicine regimens, the need for cost containment and the requirement for improving the quality of patient care [2,3]. IMM was therefore devise to optimize the medicines management system in hospital by maximizing the input of both pharmacists and pharmacy technicians as part of the multidisciplinary team to the process. The benefits of the new service include reduced length of stay (LOS), reduced number of readmissions [5–7] and an improvement in the medication appropriateness index [8]. When adopted in a Swedish hospital, the IMM programme yielded similar benefits [9,10].

The robust targeting of resources to patients who are most in need of health care services is expected to lead to both improved overall quality and cost-effectiveness of health care. Hospital readmission rate is considered as one measure that indicates hospital service effectiveness [11]. Most hospital admissions involve patients with chronic illnesses, e.g. cardiac and respiratory system diseases [12–14]. It has been shown that as few as 2% of patients with long-term conditions are responsible for 30% of hospital

emergency admissions, many of which are avoidable [15]. These data highlight the need for targeted hospital services, especially for higher risk patients.

Risk of re-hospitalization is highly associated with other standard outcome measures, such as mortality, LOS and cost [16]. To improve patient targeting, the Department of Health has recommended the use of a case finding medical algorithm called patients at risk of re-hospitalization (PARR) [12–14]. PARR++ is a computerized, predictive algorithmic modelling tool, developed by the King's Fund, which gives risk scores for re-hospitalization of individual patients in the 12 months post-discharge [17].

PARR can be considered as a risk-adjusted quality measure that takes account of both patient severity of illness and current circumstances. Other risk measures used within the sector are risk-adjusted mortality index (RAMI) and risk-adjusted LOS index (RALI). As a predictive tool, RAMI was developed to calculate the risk of death during inpatient stay based on a range of variables, that is age, gender, diagnosis-related group, diagnosis and specific co-morbidities within the population being investigated [18,19]. RAMI has also been shown to be a good quality indicator for outpatients receiving ambulatory care services [20], in which the clinical pharmacist can also play an essential role [21]. RALI is a useful health care quality indicator enabling better comparisons between hospitals and their performance over time [22–24].

The main aim of the present study was to further explore factors that influence risk of readmission and post-discharge mortality enabling the targeting of clinical pharmacy services based on a risk-predictive model.

Methods

The study was conducted in Antrim Area Hospital (426 beds), a teaching hospital within the Northern Health and Social Care Trust in Northern Ireland. A cohort of patients who had received the IMM service at the hospital ($n = 806$) were included in the study and were part of a broader research project on health care outcomes, approved by the Office of Research and Ethical Committees in Northern Ireland (reference number 05/NI01/98).

Data required to calculate the assessment measures were obtained from hospital episode statistics, including demographic data, diagnoses and admission stay and were retrieved by the corporate information department at the hospital. The raw data were received in a format enabling importation into the PARR++ version 3.5.5 programme. Running the monthly PARR++ algorithm produced PARR re-hospitalization risk scores as PARR scores of 0–100, grouped per month of admission. The total number of months covered was 60, that is, all relevant admissions over a 5-year period were included. All patients were followed up for a period of 12 months post-discharge. The measures used to follow patients during the study (i.e. during their inpatient stay and during 12 months post-discharge) are highlighted in Table 1.

Co-morbidity was calculated for each admission case using the Charlson index [25]. Accordingly, the primary and secondary admission diagnoses were included in each co-morbidity calculation based on the International Classification of Diseases 10 coding system.

The RAMI and RALI were calculated by CHKS Ltd. (Warwickshire, UK), a specialist company that provides benchmarking and analytical services to the UK National Health Service. RAMI and RALI were calculated by CHKS for all patients included in the study using a multiple regression algorithmic model. Hospital mortality probability and expected LOS for the patients were risk adjusted for age, sex, diagnoses, procedures, clinical grouping and admission type. RAMI was calculated as a value between 0 and 100% as a risk of death, while RALI, being predicted risk-adjusted length of in-hospital stay, had days as the LOS unit. Age-adjusted co-morbidity was calculated by combining the age factor with Charlson co-morbidity index variables; the score for a patient was the summation of the Charlson co-morbidity score and one risk point added for each decade of age over 40 [26,27].

Clinical pharmacy staffing data were retrieved from the pharmacy staffing database at the hospital. The staffing data included details about the clinical pharmacy team members, that is, pharmacists and technicians, and their full-time equivalent (FTE) values. FTEs for the staff were calculated on a monthly basis taking staff turnover into account.

All data were transferred into PASW® statistics (SPSS, IBM, Portsmouth, UK) for windows (version 18.0) to perform statistical analysis. Standard statistical methodologies were used to explore

Table 1 Assessment measures used in modelling process

Assessment measures
a) Hospital readmission measures:
1 Incidence of emergency admission at 1, 3, 6 and 12 months post-discharge to any of the hospitals within the NHSCT.
2 Number of readmissions to hospital within 12 months post-discharge.
3 Number of previous emergency admissions in 3 years before the index admission.
4 Patient at risk of re-hospitalization.
b) Mortality measures:
1 Mortality in the hospital or in 12 months post-discharge.
2 Risk-adjusted mortality index.
c) Hospital stay measures:
1 Length of hospital stay (LOS), calculated by subtracting admission date from discharge date.
2 Risk-adjusted length of hospital stay index (RALI).
3 Hospital standardized LOS ratio, and 150% hospital standardized LOS ratio. Hospital standardized LOS equals the actual length of stay (LOS) divided by the risk-adjusted LOS (RALI), that is, LOS/RALI.

NHSCT, Northern Health and Social Care Trust.

the data and analyse the relationships between variables. The Spearman correlation test was the test chosen to determine relationships between two continuous variables, for example, PARR score and number of emergency readmissions in the 12 months post-discharge. Dichotomous categorical-dependent variables (i.e. readmission and mortality) were analysed against dependent variables (categorical and nominal) using binary logistic regression analysis.

Univariate analysis was used as an initial step of testing differences in each variable between any two groups of patients. Different univariate tests were used depending on the characteristics of the data under investigation. The Pearson chi-square (χ^2) test was used with categorical variable data, the independent samples *t*-test was used with normally distributed continuous variable data while the Mann–Whitney *U*-test was used for non-normally distributed continuous variable data.

The predictor measures (independent variables) were considered as candidates for logistic regression modelling if they had a significance value ≤0.25. The candidate variables were subjected to 'backward' logistic regression, where finally only the significant variables (i.e. $\rho \leq 0.05$) were retained with the model equation constant.

Predictive algorithms were developed using the following equation [28].

$$\text{Probability}\,(P) = \frac{1}{1 + e^{-(B0 + B1X1 + B2X2 + \ldots + BnXn)}}$$

where $B0$ is the regression coefficient of the constant, $B1$ is the regression coefficient (weight) of the variable (predictor) $X1$, $B2$ is the regression coefficient of the variable $X2$ and so on.

To create risk-predictive algorithms, the full IMM sample of patients was divided into two sample groups, that is, development and validation. The validation sample of patients was selected using a table of random numbers and represented about 25% of the full sample. The other 75% were considered the development sample. The logistic regression predictive algorithms were created using the development sample data, and then validated using the validation sample data.

The predictive algorithms developed were applied to the validation sample and predicted risk probability was generated for each patient from the coefficients. Receiver operating characteristic (ROC) curves were then drawn. A regression algorithm was considered acceptable in predicting the risk if the area under ROC curve (ROC AUC) was ≥0.500, in comparison with a reference line. The discrimination ability of the algorithms were characterized according to ROC AUC values as follows: excellent (0.90–1.0), good (0.80–0.89), fair (0.70–0.79), modest (0.60–69) and poor (<0.60) [29–32].

Risk thresholds for the algorithms with the highest ROC AUC values were determined by identifying the cut-off points of risk scores at which the algorithm would have the highest discriminative performance. The performance was determined by the positive and negative probabilities and likelihood ratios (LRs) [32,33].

There are established benchmarks for LRs when they are used to assess the performance of predictive algorithms [33]. The predictive ability of the algorithms was characterized using the following approach: excellent and often conclusive ($LR > 10.0$), good ($5.0 \leq LR \leq 10.0$), fair but sometimes important ($2.0 \leq LR \leq 4.9$) and poor ($1.0 \leq LR \leq 1.9$).

Results

The study included 806 patients (Fig. 1). Risk scores for the IMM patients, that is, PARR, RAMI and RALI, along with their LOS and Charlson co-morbidity index scores are shown in Table 2. Patient characteristics of the development ($n = 605$) and validation ($n = 201$) samples are shown in Table 3. Taking into consideration the relatively small size of the validation sample, the small differences in characteristics between the two groups was considered acceptable.

Risk-predictive algorithms

Risk of mortality (in-hospital and 12-month post-discharge)

During the course of the study 21.6% IMM patients died. Univariate statistical tests were initially performed to examine the individual relationship between 26 variables and the dependent variable of mortality (in-hospital and post-discharge). Seventeen variables had relationships with mortality with $\rho \leq 0.25$. Backward logistic regression involving the 17 variables versus the dependent variable resulted in three variables: age-adjusted co-morbidity index score, ACE inhibitors or ARBs and number of previous admissions in 3 years remain in the model. Odds ratios associated with the model (algorithm) are presented in Table 4.

The created predictive algorithm had the following mortality probability (P) equation:

$$P(\text{In-hospital and 12-month post-discharge mortality}) = \frac{1}{1 + e^{-(-4.664 + 0.484X1 + 0.501X2 + 0.139X3)}}$$

where $X1$ is the age-adjusted co-morbidity score, $X2$ is ACE inhibitors and ARBs, and $X3$ is number of previous admissions in 3 years. The Hosmer and Lemeshow test showed a chi-square value of 0.973 for the backward logistic regression final step, showing a non-significant ($\rho = 0.998$) difference between the observed data and the predicted values.

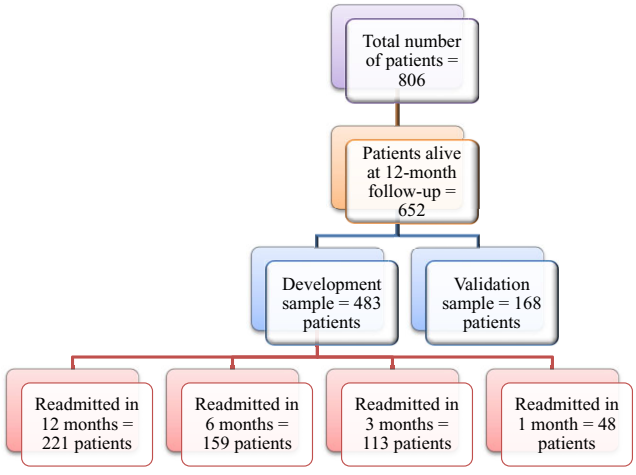

Figure 1 The number of patients involved in developing and testing of the risk of hospital readmission algorithms.

Table 2 Risk scores, LOS and co-morbidity and age-adjusted co-morbidity scores

		95% CI		Percentiles		
	Mean	Lower	Upper	25%	50% (Median)	75%
PARR	20.12	19.21	21.04	10.73	17.14	25.62
RAMI	7.47	6.57	8.38	1.49	3.47	8.01
RALI	7.69	7.36	8.02	4.95	7.71	10.54
LOS	14.17	12.73	15.61	4.00	8.00	14.00
Co-morbidity index	1.26	1.17	1.36	0.00	1.00	2.00
Age-adjusted co-morbidity	4.68	4.54	4.83	3.00	5.00	6.00

CI, confidence interval; LOS, length of hospital stay; PARR, patient at risk of re-hospitalization; RALI, risk-adjusted length of hospital stay index; RAMI, risk-adjusted mortality index.

Based on the model equation, new predicted scores of risk of mortality were created for the validation sample. Accordingly, a ROC curve was drawn to evaluate the ability of the model in risk prediction. The AUC was 0.736 (95% confidence interval = 0.647–0.826). It was significant at >0.5 ($P \leq 0.001$), indicating fair model discrimination.

ROC curve AUC values for the other measures available for use at the admission stage for the validation sample are shown in Table 5. Age, co-morbidity score and age-adjusted co-morbidity score, in addition to the created mortality-predictive algorithm, had statistically significant AUC values ≤0.5. The number of previous emergency admissions and number of admission medicines failed to be good predictive tools for risk of in-hospital and 12-month post-discharge mortality.

The likelihood probabilities for patients to die (likelihood+) and to survive (likelihood–) during hospital stay and 12-month post-discharge were generated for each risk score point in both the mortality algorithm and age-adjusted co-morbidity index. Accordingly, the LR for mortality probability prediction was calculated from the ratio of likelihood+ to likelihood– at each score point.

A number of mortality algorithm risk scores had a LR >6.0, indicating an increased risk of mortality predictive ability and can be used as cut-off points or risk thresholds (Fig. 2). The highest LR cut-off point was a risk score 6 (LR = 8.8). Another three risk scores, 10, 33 and 42 (LR = 8.2, 7.1 and 7.3, respectively), can also be considered as good risk thresholds.

However, the age-adjusted co-morbidity index had a main cut-off point at score 8 (LR = 11.4), at which and above an excellent and often conclusive mortality predictive ability was noted (Fig. 3). Another cut-off point at the age-adjusted co-morbidity index was score 4 (LR = 7.2), which had good mortality predictive ability.

Risk of readmission within 12 months

Univariate statistical tests were initially performed to examine the individual relationship between 26 variables and the dependent variable of readmission within 12 months. Thirteen variables had relationships with 12-month hospital emergency readmission with $\rho \leq 0.25$. Backward logistic regression involving the 13 variables versus the dependent variable resulted in two variables remaining in the final model; the total number of admission medicines and number of previous admissions in 3 years pre-admission.

The likelihood probabilities for patients to be re-hospitalized (likelihood+) and not to be re-hospitalized (likelihood–) in the 12 months post-discharge were generated for each risk score point in the readmission algorithm. Accordingly, the LR for the 12-month post-discharge hospital readmission probability prediction was calculated from the ratio of likelihood+ to likelihood– at each score point.

Three main cut-off points on the readmission algorithm scale were denoted at 64, 72 and 80 risk scores (LR = 2.7, 3.0 and 3.5, respectively), indicating a fair, but sometimes important, risk of 12-month post-discharge hospital readmission predictive ability at these points and above, and can be used as risk thresholds (Fig. 4).

The PARR algorithm was better than the other tested parameters except the algorithm created in this study and the number of previous admissions (in 3-year period before index admission) parameter.

The created predictive algorithm had a moderate positive effect correlation with the number of emergency hospital admissions 12 months post-discharge. Spearman's rho correlation coefficient was 0.260 ($\rho \leq 0.001$). The number of previous emergency admissions in 3 years and to a lesser extent the PARR score also had a statistically significant moderate positive effect correlation (Table 6).

Risk of hospital readmission in a period of ≤6 months post-discharge

The same prediction algorithm was tested against 6-month hospital readmission data of the validation sample patients. AUCs of 6-month ROC curves were significantly ≥0.5 (0.636), indicating modest model discrimination.

The likelihood probabilities for the patients to be re-hospitalized (likelihood+) and not to be re-hospitalized (likelihood–) in the 6 months post-discharge were generated for each risk score point in the readmission algorithm, and the LR for the 6-month post-discharge hospital readmission probability prediction was calculated from the ratio of likelihood+ to likelihood– at each score point.

The cut-off points 6-month risk of readmission were 64 and 80 risk scores, and matched with the 12-month readmission risk thresholds. The risk threshold 80 for 6-month readmission prediction had a good predictive ability (Table 7).

Risk of post-discharge mortality or readmission

The total number of patients who died or were readmitted to the hospital in the 12-month post-discharge period was 395 (49% of the study patients). Fifteen variables had relationships with 12-month post-discharge mortality or hospital emergency read-

Table 3 Patient characteristics of the development and validation samples

Variable	Development (n = 605)	Validation (n = 201)
Age (mean)	69.1	70.1
Co-morbidity index score (mean)	1.3	1.2
Age-adjusted co-morbidity (mean)	4.7	4.7
Gender	51.8% male : 48.2% female	49.8% male : 50.2% female
Previous admissions (mean)	2.8	2.3
Mortality (%)		
- During hospital stay	2.3	3.5
- During study period	19.9	16.4
PMH (system categories) (%)		
- Circulatory	67.5	72.1
- Endocrine/nutritional/metabolic	20.2	37.8
- Respiratory	26.8	28.4
- Musculoskeletal	21.9	19.4
- Surgery/fracture/fall	20.2	18.9
- Nervous/mental/behavioural	17.7	19.9
- Genitourinary	13.1	15.9
- Digestive	13.6	12.4
- Neoplasm	9.8	11.4
- Other*	8.9	10.0
Medicines		
- ≥4 drugs on admission (%)	88.2	87.6
- Number of admission medicines (mean)	7.5	7.5
High-risk medicines (%)		
- NSAIDs	36.9	40.3
- ACE inhibitors and ARBs	35.1	35.3
- Diuretics	36.3	37.3
- β-Blockers	31.6	32.8
- Digoxin	10.8	10.9
- Clopidogrel	10.4	10.0
- Antidepressants	17.9	14.9
- Warfarin	8.9	11.9
- Prednisolone	4.6	2.5
- Opiates	16.6	12.9
- Any of the high-risk medicines	80.3	82.1
Clinical pharmacy interventions (%)		
- Admission stage	74.0	75.6
- Inpatient stage	59.3	62.2
LOS (mean)	14.5	13.2
PARR score (mean)	20.5	19.0
RAMI (mean)	7.4	7.8
RALI (mean)	7.9	7.3
LOS > RALI (%)	49.0	47.3

*Other systems (e.g. skin and soft tissues, blood, infectious disease, eye and ear).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LOS, length of hospital stay; NSAID, non-steroidal anti-inflammatory drug; PARR, patient at risk of re-hospitalization; PMH, past medical history; RALI, risk-adjusted length of hospital stay index; RAMI, risk-adjusted mortality index.

mission with $\rho \leq 0.25$. Backward logistic regression involving the 15 variables versus the dependent variable resulted in age-adjusted co-morbidity score, receiving diuretics, both number of admission medicines and previous admissions in 3 years pre-admission remaining in the model.

The likelihood probabilities for patients to die or to be re-hospitalized (likelihood+) and to survive or not to be re-hospitalized (likelihood–) in 12 months post-discharge were generated with the LR for each risk score point in the readmission algorithm. One main cut-off point on the post-discharge mortality and readmission algorithm scale was present at risk score 83 (LR = 4.0), indicating a fair, but sometimes important, risk of 12-month post-discharge mortality or readmission predictive ability at these points and above and can be used as a risk threshold.

Table 4 Odds ratios of the final parameters included in the logistic regression predictive model of mortality (in-hospital and 12-month post-discharge) for the development sample

Variable	B (SE)	Odds ratio	95% CI	ρ
Constant	–4.66 (0.44)			**<0.001***
Age-adjusted co-morbidity	0.48 (0.06)	1.62	1.44–1.83	**<0.001***
ACE inhibitors and ARBs	0.50 (0.25)	1.65	1.02–2.67	**0.042***
Previous admissions	0.14 (0.04)	1.15	1.07–1.24	**<0.001***

*Significant difference, $\rho \leq 0.05$.
Boldface represents significant results.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; SE, standard error.

Table 5 AUCs of the predictive algorithm and other measures available at admission on prediction of mortality (in-hospital and 12-month post-discharge)

Variable	Area (SE)	95% CI	Significance (ρ)
Mortality algorithm	0.74* (0.05)	0.65–0.83	**<0.001†**
Age	0.61* (0.05)	0.51–0.72	**0.043†**
Co-morbidity	0.70* (0.06)	0.59–0.81	**<0.001†**
Age-adjusted co-morbidity	0.75* (0.05)	0.67–0.84	**<0.001†**
Total number of medicines on admission	0.50* (0.06)	0.39–0.61	0.975
Number of previous admissions	0.52* (0.05)	0.42–0.62	0.730

*Area ≥ 0.5.
†Significant difference, $\rho \leq 0.05$.
Boldface represents significant results.
AUC, area under curve; CI, confidence interval; SE, standard error.

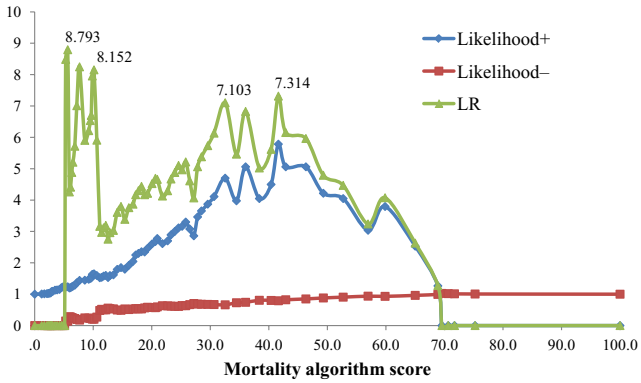

Figure 2 Likelihood ratios (LR) profile and suggested cut-off points for the mortality algorithm risk scores.

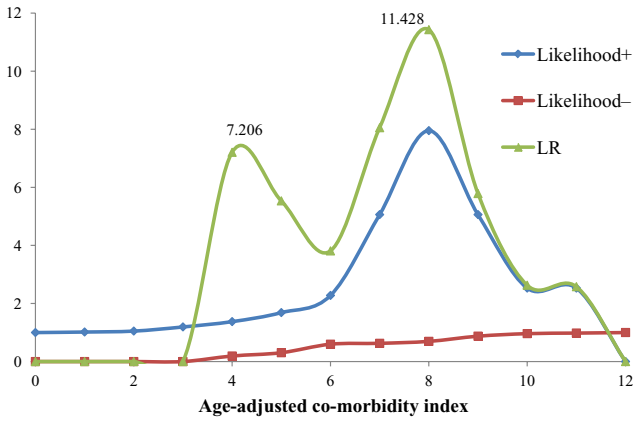

Figure 3 Likelihood ratios (LR) profile and suggested cut-off points for the age-adjusted co-morbidity index risk scores in predicting mortality.

Risk of post-discharge mortality

The same prediction algorithm, developed for use on admission based on in-hospital and post-discharge mortality data (mortality algorithm), was tested against the post-discharge mortality data of the validation sample.

The likelihood probabilities for patients to die (likelihood+) and to survive (likelihood–) 12-month post-discharge were generated for each risk score point in the mortality algorithm and the age-adjusted co-morbidity index. The LR for mortality probability prediction was calculated for each score point.

There were three main cut-off points suitable to be considered as risk thresholds. The risk score with the highest LR was at and above 35 (LR = 5.3), and it had a good risk of mortality-predictive ability. The other two cut-off points were at-risk scores 46 and 69 (LR = 4.9 and 4.6, respectively), with a fair, but sometimes important, mortality risk-predictive ability.

On the other hand, the age-adjusted co-morbidity index had a main cut-off point at score 4 (LR = 11.1), at which and above an excellent and often conclusive mortality predictive ability was noted. Another cut-off point at the age-adjusted co-morbidity index was score 8 (LR = 8.7), which had good mortality-predictive ability.

Relationship between clinical pharmacy staffing and the study measures

The clinical pharmacy team initially consisted of four clinical pharmacists (3.1 FTEs) and 10 clinical pharmacy technicians (9.1

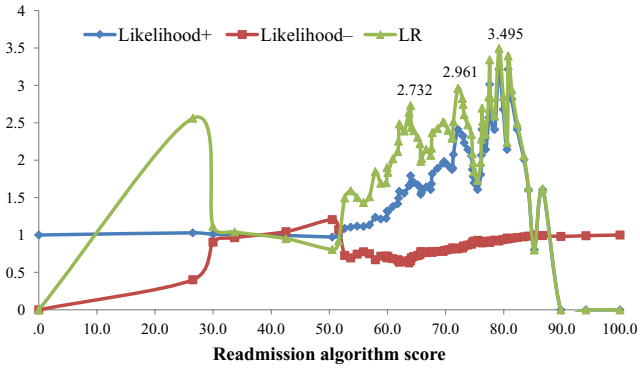

Figure 4 Likelihood ratios (LR) profile and suggested cut-off points of the readmission algorithm risk scores for 12-month post-discharge hospital readmission.

FTEs) in October 2003 (at the initiation of IMM), but increased to 18 clinical pharmacists (16.9 FTEs) and 15 clinical pharmacy technicians (13.6 FTEs) in September 2008. Total FTEs for the clinical pharmacy team increased from 12.2 to 30.5 over the 5-year study period. Correlation between monthly FTEs and monthly mean scores for study measures was analysed using the two-tailed Spearman's correlation test. Findings are shown in Table 8.

Total FTE, FTE for pharmacists and FTE for clinical pharmacy technicians showed significant negative relationships with hospital LOS mean results. The relationship between LOS and the three FTE categories was strong in effect size (in all clinical pharmacy staffing FTE categories, $r = -0.65$ and $\rho = <0.01$). Clinical pharmacy staffing FTEs also had a significant, negative and moderate strength correlation with co-morbidity index ($r = -0.34$, $\rho = <0.01$) and RAMI ($r = -0.28$, $\rho = <0.05$) mean monthly scores (Fig. 5).

Although no significant relationship was present between the FTEs and PARR mean monthly scores, total clinical pharmacy staffing FTEs and pharmacist FTEs had a medium-positive relationship with RALI mean monthly scores (RALI versus total staff FTEs and pharmacist FTEs, $r = 0.34$, $\rho = <0.01$; and RALI versus technician FTEs, $r = 0.31$, $\rho = <0.05$).

Discussion

Combining routine inpatient data with patient medications and derived data from existing algorithms can be used to develop new case-finding algorithms for patients at high risk of readmission, mortality and longer hospital stay.

A number of independent variables had previously been shown to have a relationship with patient outcomes and were used to construct the targeting criteria for the IMM service [6]. Age-adjusted co-morbidity index scores were calculated for each patient and included in the present research to evaluate the relationship between severity of illness and outcome measures [26,27].

For the admission stage risk-predictive algorithms, those variables associated with patient admission were included in the analyses, as the objective was to create risk-predictive tools (algorithms) for clinical pharmacy team targeting. This concept was applied to discharge stage statistical analyses. More variables are available to be used at discharge stage, for example, LOS and inpatient interventions, for algorithm creation.

Risk of longer hospital stay than expected

An algorithm predicting risk of longer hospital stay than expected could not be created using the available IMM development sample patient data. At the same time, other measures, that is, age, Charlson co-morbidity index score, age-adjusted Charlson co-morbidity score, number of admission medicines and previous admissions, failed to reach the thresholds by which they could be considered good predictive algorithms for longer than expected hospital LOS. Separate age and co-morbidity results, however, have been shown to significantly correlate with LOS predictions [19,34].

Risk of mortality

IMM patients who died during their hospital stay or in the 12 months after discharge were characterized by having at least one of the following characteristics: had a larger age-adjusted co-morbidity score, in other words they were older and/or more chronically ill than other patients; were receiving an ACE inhibitor or an ARB on admission; and had more frequent previous emergency admissions to the hospital in the 3 years before the index admission.

The positive relationship between the age-adjusted co-morbidity score in this algorithm and the predicted mortality was expected and supported by the literature [26,27,35].

Although ACE inhibitors and ARBs have a protective role post-myocardial infarction and protect against stroke [36,37], the algorithm developed indicated that patients who were receiving ACE inhibitors or ARBs on admission were at higher risk of mortality than other patients. It is expected that the high mortality rate was related to the seriousness of diseases that this group of medicines is aimed to treat, for example, heart failure, stroke and diabetic nephropathy [38]. Such diseases have high morbidity and mortality [39]. Therefore, mortality is likely to be linked to illness and its severity rather than receipt of medicines *per se*. It is noteworthy, however, that when added to the algorithm, they increased its predictive ability.

Previous emergency admissions in the last 3 years was an important factor within the final model. Frequent admission to hospital indicates a relatively more complicated or less stable medical case, which is predicted to play a significant role, not only in increasing the risk of mortality but also the risk of future readmission after discharge [16].

The developed mortality algorithm could successfully discriminate the odds of deaths both inside and outside the hospital. Although this incorporated data about patients' medicines, there was no obvious difference in mortality prediction performance when compared with the age-adjusted Charlson co-morbidity index. The two approaches had a fair mortality predictive ability, according to the ROC AUC data, that is, in both cases these were significantly >0.70.

Four cut-off points were identified on the mortality algorithm risk scale. All had good discriminative ability and can be used to classify patients according to their level of risk of mortality. On the other hand, the age-adjusted co-morbidity index had two cut-off

Table 6 Correlation of number of 12-month emergency readmissions with the predictive algorithm score, number of previous admissions and PARR score

	Number of 12-month hospital emergency readmissions	
	r	ρ
12-month predictive algorithm risk score	0.260	**<0.001***
Number of previous emergency admissions over 3-year period prior to index admission	0.246	**<0.001***
PARR score	0.185	**<0.001***

*Significant difference, ρ ≤ 0.01.
Boldface represents significant results.
PARR, patient at risk of re-hospitalization.

Table 7 Performance of the 12-month readmission algorithm in predicting readmission in 12, 6 and 3 months post-discharge

	Risk threshold	Sensitivity	Specificity	False positive	False negative	Likelihood+	Likelihood–	LR
12-month readmission	**64%**	54.2	69.8	30.2	45.8	1.8	0.7	2.7 (fair)
	80%	11.2	96.5	3.5	88.8	3.2	0.9	3.5 (fair)
6-month readmission	**64%**	65.6	65.0	35.0	34.4	1.9	0.5	3.6 (fair)
	80%	9.4	98.1	1.9	90.6	4.8	0.9	5.2 (good)
3-month readmission	**64%**	62.8	66.1	33.9	37.2	1.9	0.6	3.3 (fair)
	80%	9.3	96.8	3.2	90.7	2.9	0.9	3.1 (fair)

Boldface represents significant results.
LR, likelihood ratio.

Table 8 Correlation between the clinical pharmacy team FTEs and the study measures

		Total FTEs	Pharmacist FTE	Technician FTE
PARR	*r*	0.126	0.104	0.121
	Sig. ρ	0.336	0.430	0.358
Co-morbidity index	*r*	–0.348	–0.336	–0.399
	Sig. ρ	0.006†	0.009†	0.002†
RAMI	*r*	–0.285	–0.281	–0.278
	Sig. ρ	0.027*	0.029*	0.031*
RALI	*r*	0.344	0.346	0.311
	Sig. ρ	0.007†	0.007†	0.015*
LOS	*r*	–0.650	–0.653	–0.653
	Sig. ρ	<0.001†	<0.001†	<0.001†

*Significant correlation at ρ ≤ 0.05.
†Significant correlation at ρ ≤ 0.01.
FTE, full-time equivalent; LOS, length of hospital stay; PARR, patient at risk of re-hospitalization; RALI, risk-adjusted length of hospital stay index; RAMI, risk-adjusted mortality index.

points at score 4 (good discrimination) and score 8 (excellent discrimination). Again these can be used to classify the patients into low, high and very high risk of in-hospital and 12-month post-discharge mortality. A direct comparison of the predictive performance of the different approaches could not be carried out at specific risk thresholds because the score scales had a different pattern.

Risk of post-discharge mortality

Mortality in the 12 months post-discharge was studied separately for the purpose of targeting the discharge stage clinical pharmacy service to patients at higher risk of mortality. The same mortality algorithm was validated on data relating to patients who died after discharge.

The mortality algorithm performed better in predicting risk of post-discharge death than predicting mortality in general. The algorithm developed had the same predictive power as the age-adjusted Charlson co-morbidity score. As mentioned earlier, the age-adjusted co-morbidity score would be a more convenient targeting tool for identifying patients at higher risk of mortality for clinical pharmacy intervention in routine practice, as this score is easier to calculate than the algorithm developed during the present study.

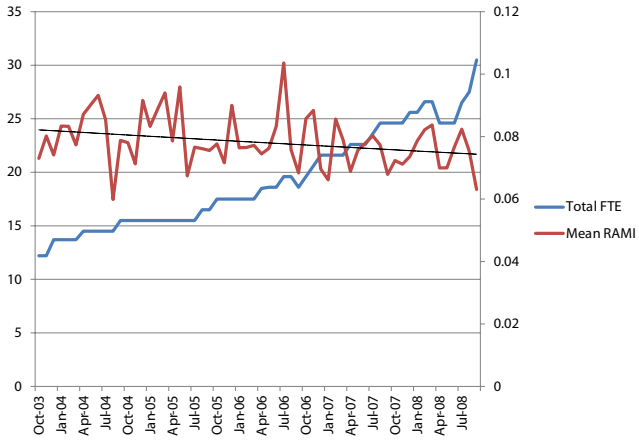

Figure 5 Relationship between total pharmacy full-time equivalents (FTEs) and mean risk-adjusted mortality index (RAMI).

Other measures and algorithms, that is, the Charlson co-morbidity index score (not age adjusted), LOS and RAMI also successfully predicted risk of post-discharge mortality; however, these approaches did not yield as good a predictive power as the mortality algorithm developed during this study and the age-adjusted Charlson co-morbidity score. Although the mortality algorithm performed better than RAMI, it should be pointed out that RAMI was designed to predict only risk of in-hospital mortality.

Three cut-off points were identified on the mortality algorithm risk scale as risk thresholds for 12-month post-discharge mortality, while the age-adjusted co-morbidity index had the same two cut-off points (i.e. scores 4 and 8). The age-adjusted Charlson co-morbidity index had stronger cut-off points (i.e. higher LR) predicting post-discharge mortality than the mortality algorithm risk thresholds, although the two scales had a different risk score pattern.

Risk of emergency hospital readmission

Risk of hospital readmission in the 12 months post-discharge

Patient characteristics retained in the 12-month readmission prediction algorithm derived during this research were:

1 Number of medicines patient was receiving at time of admission.

2 Number of previous emergency admissions to the hospital in the 3 years before the index admission.

The receipt of four or more medicines is a sign of significant co-morbidity. Polypharmacy patients are also more susceptible to ADRs, which if serious can lead to hospitalization [40–42].

It was not surprising that previous hospital admissions in the past 3 years remained as a parameter within the final algorithm. Previous admission to hospital is a well-known major risk factor for emergency hospital readmission [43]. It is used in the PARR++ algorithm that was specifically designed to flag patients at risk of emergency readmission in the 12-month period post-discharge [17].

Both the 12-month readmission algorithm and the number of previous readmissions alone had very similar ROC AUC values. Nevertheless, other measures and risk algorithms, including PARR score, did not show a satisfactory predictive strength in the present population (low ROC AUC values). This finding was unexpected as PARR was specifically designed, via extensive research, to reflect 12-month readmission probabilities, and has been found by others to have reliable predictive performance [12,32]. The number of future emergency admissions 12 months after the index discharge showed a significant direct correlation with PARR risk score; however, the correlation was stronger with the created readmission algorithm and the number of previous emergency admissions.

Risk of hospital readmission in a period of ≤6 months post-discharge

The readmission algorithm was tested for its ability in predicting risk of readmission within 6, 3 and 1 month. Together with the number of previous emergency admissions over the prior 3 years, the algorithm was valid in predicting readmission within 6 months. It could also predict risk of readmission within 3 months, that is, ROC AUC values in both cases were significantly greater than 0.5, while the number of previous admissions alone could not.

The model failed to have a valid prediction performance for risk of 1-month readmission. However, the best performance was in predicting 6-month readmission. Other measures and algorithms, including PARR, could not correctly predict risk of readmission at 1, 3, 6 and 12 months post-discharge.

The readmission algorithm had two cut-off points in common with the 12-month prediction findings (i.e. risk scores of 64 and 80) when predicting 3- and 6-month post-discharge risk of readmission. Accordingly, the readmission risk algorithm can be used to classify patients based on their risk of emergency hospital readmission, up to 12 months post-discharge, into three groups: low-risk patients (score <64), high-risk patients (score ≥64 and <80) and very high-risk patients (score ≥80).

Risk of post-discharge mortality or readmission

Patient characteristics retained in the 12-month mortality or readmission risk prediction algorithm were:

1 Number of medicines a patient was receiving at time of admission.

2 Number of previous emergency admissions to the hospital in the 3 years before the index admission.

3 The age-adjusted co-morbidity index score.

4 Patient receiving a diuretic at time of admission.

The new variable within this algorithm is receiving a diuretic at time of admission. Diuretics are known to have significant side effects, in particular hypokalaemia. Receipt of diuretics is well known as a risk factor for re-hospitalization [38,44,45], and thus, it was surprising that this parameter was not retained in any of the previous models.

One cut-off point was identified on the mortality or readmission algorithm risk scale as a risk threshold for 12-month post-discharge mortality or emergency hospital readmission. This cut-off point was risk score 83, and it had a fair discriminating ability.

Prospective benefits of risk-predictive algorithms

Effective implementation of the risk-predictive algorithms developed and validated in this research would enable patients to be categorized according to their relative risk of mortality, readmission or both, during their in-hospital and post-discharge, according to the risk thresholds (cut-off points).

In the present context, patients with the highest risk would therefore be prioritized to receive clinical pharmacy services.

Effect of clinical pharmacy staffing number on the study measures

The change in numbers of both clinical pharmacists and technicians calculated as FTEs represents the quantitative change in clinical pharmacy service input. In other studies, clinical pharmacist numbers were found to be associated with a decreased LOS [46,47], medication errors and adverse drug reactions [47,48], and hospital mortality rates [46,47,49]. The number of both clinical pharmacists pharmacy technicians per 100 occupied hospital beds was also indirectly associated with a reduced severity of illness-adjusted hospital mortality rates [46], including RAMI scores. Clinical pharmacy staff and technicians are heavily involved in IMM process that has already demonstrated positive findings, for example, decreased LOS and readmission rate [6,7]. This analysis has demonstrated that the provision of pharmacy services at ward level is correlated with a decrease in monthly mean RAMI scores that is in line with the US data referenced above.

Limitations and strengths

Limitations

Although the sample size was large in terms of intervention studies, it was relatively small in terms of epidemiology investigations. Unfortunately, data on FTE staffing levels for medical and nursing staff were not available to include in the analysis. The overall risk assessment tool(s) is complex as it included scores from other algorithms, that is, PARR, RAMI and RALI. Finally, consideration of case-mix changes over the analysis period could have been improved.

Strengths

The fact that this paper can be linked to the beneficial outcomes of the IMM project, as exemplified by the earlier publications, adding weight to the findings that this intervention is a key component in terms of medicines optimization. The analysis is based on a distinctive patient sample who received the IMM service versus a sample who did not; this mitigates the variability in other parameters such as nurse staffing levels that may have changed over the time period covered.

References

1. Department of Health (2000) Pharmacy in the future – implementing the NHS plan. London: Department of Health.
2. The Audit Commission (2001) A spoonful of sugar: medicines management in NHS hospitals. Available at: http://www.audit-commission.gov.uk/SiteCollectionDocuments/AuditCommissionReports/NationalStudies/nrspoonfulsugar.pdf (last accessed 27 May 2008).
3. Fleming, G. F., Hogg, A., Woods, A., Scott, M. G. & McElnay, J. C. (2003) A hospital-based integrated medicines management model. *The Pharmaceutical Journal*, 271, 214–215. Available at: http://www.pharmj.com/pdf/articles/pj_20030816_hospitalbased.pdf (last accessed 4 October 2007).
4. Smith, J. (2004) Building a safer NHS for patients: improving medication safety. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4084961.pdf (last accessed 3 March 2010).
5. Scott, M. & Clark, C. (2002) Integrated medicines management breaks new ground in N. Ireland. Available at: http://www.evidence.nhs.uk/document?ci=http%3A%2F%2Fwww.pharmj.com%2Fpdf%2Fmm%2F200205%2Fmm_200205_newground.pdf%3Ffromsource%3Dnelm&q=integrated%20test&ReturnUrl=%2Fsearch%3Fq%3Dintegrated%2520test%26ps%3D30%26pa%3D6 (last accessed 4 October 2007).
6. Scullin, C., Scott, M. G., Hogg, A. & McElnay, J. C. (2007) An innovative approach to integrated medicines management. *Journal of Evaluation in Clinical Practice*, 13, 781–788.
7. Scullin, C., Hogg, A., Luo, R., Scott, M. G. & McElnay, J. C. (2012) Integrated medicines management – can routine implementation improve quality? *Journal of Evaluation in Clinical Practice*, 18, 807–815.
8. Burnett, K. M., Scott, M. G., Fleming, G. F., Clark, C. M. & McElnay, J. C. (2009) Effects of an integrated medicines management program on medication appropriateness in hospitalized patients. *American Journal of Health-System Pharmacy*, 66, 854–859.
9. Bergkvist, A., Midlov, P., Hoglund, P., Larsson, L., Bondesson, A. & Eriksson, T. (2009a) Improved quality in the hospital discharge summary reduces medication errors – LIMM: Landskrona Integrated Medicines Management. *European Journal of Clinical Pharmacology*, 65, 1037–1046.
10. Bergkvist, A., Midlov, P., Hoglund, P., Larsson, L. & Eriksson, T. (2009b) A multi-intervention approach on drug therapy can lead to a more appropriate drug use in the elderly. LIMM-Landskrona Integrated Medicines Management. *Journal of Evaluation in Clinical Practice*, 15, 660–667.
11. Martin, L. A., Nelson, E. C., Lloyd, R. C. & Nolan, T. W. (2007) Whole system measures – IHI innovation series white paper. 16, Institute for Healthcare Improvement. Available at: http://www.ihi.org/NR/rdonlyres/F87FED3F-FEB5-4E52-9F74-39399D8F7080/0/IHIWholeSystemMeasuresWhitePaper2007.pdf (last accessed 25 February 2010).
12. Billings, J., Dixon, J., Mijanovich, T. & Wennberg, D. (2006) Case finding for patients at risk of readmission to hospital: development of algorithm to identify high risk patients. *BMJ (Clinical Research Ed.)*, 333, 327.
13. Webb, M. (2006) Rapid overview of the evidence on the use of predictive risk tools in chronic disease management. National Public Health Service of Wales. Available at: http://www2.nphs.wales.nhs.uk:8080/healthserviceqdtdocs.nsf/($all)/9237c2d7690c06298025719d0038006f/$file/predictive%20risk%20tools%20in%20chronic%20disease%20managementv3.doc (last accessed January 2008).
14. Sriram, M. G., Rodriguez, J. R., Johnson, K. A., Kantor, G., Svirbely, J. R. & Smith, J. W. (2009) Implementing medical algorithms for use in cardiology. *Biongeniería e Informática Médica – Bioengineering/Medical Informatics*. Available at: http://www.fac.org.ar/tcvc/llave/c236/sriram.PDF (last accessed 21 January 2010).
15. Goodwin, N. & Curry, N. (2008) Methods for predicting risk of emergency hospitalisation: promoting self-care and integrated service

responses in the home to the most vulnerable. *International Journal of Integrated Care*, 8 (Suppl.), e17.
16. Curry, N., Billings, J., Darin, B., Dixon, J., Williams, M. & Wennberg, D. (2005) Predictive risk project – literature review. NHS Modernisation Agency, King's Fund, New York University, and Haelth Dialog. Available at: http://www.business.auckland.ac.nz/Portals/4/Dept/Economics/General/2009/PredRiskProjectLitReviewJune2005.pdf (last accessed 21 January 2010).
17. King's Fund, NHS, Department of Health, NYU – Robert F. Wagner Graduate School of Public Service & Health Dialog UK Limited (2007) PARR++ help notes. 03.05.05.
18. Thomas, J. W., Holloway, J. J. & Guire, K. E. (1993) Validating risk-adjusted mortality as an indicator for quality of care. *Inquiry: A Journal of Medical Care Organization, Provision and Financing*, 30, 6–22.
19. DesHarnais, S. I., Forthman, M. T., Homa-Lowry, J. M. & Wooster, L. D. (2000) Risk-adjusted clinical quality indicators: indices for measuring and monitoring rates of mortality, complications, and readmissions. *Quality Management in Health Care*, 9, 14–22.
20. Selim, A. J., Berlowitz, D. R., Fincke, G., Rosen, A. K., Ren, X. S., Christiansen, C. L., Cong, Z., Lee, A. & Kazis, L. (2002) Risk-adjusted mortality rates as a potential outcome indicator for outpatient quality assessments. *Medical Care*, 40, 237–245.
21. Yuan, Y., Hay, J. W. & McCombs, J. S. (2003) Effects of ambulatory-care pharmacist consultation on mortality and hospitalization. *The American Journal of Managed Care*, 9, 45–56.
22. Brownell, M. D. & Roos, N. P. (1995) Variation in length of stay as a measure of efficiency in manitoba hospitals. *CMAJ: Canadian Medical Association Journal = journal de l'Association medicale canadienne*, 152, 675–682.
23. Rosenthal, G. E. (1997) Weak associations between hospital mortality rates for individual diagnoses: implications for profiling hospital quality. *American Journal of Public Health*, 87, 429–433.
24. Thomas, J. W., Bates, E. W., Hofer, T., Perkins, A., Foltz-Murphy, N. & Webb, C. (1998) Interpreting risk-adjusted length of stay patterns for VA hospitals. *Medical Care*, 36, 1660–1675.
25. Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., Saunders, L. D., Beck, C. A., Feasby, T. E. & Ghali, W. A. (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care*, 43, 1130–1139.
26. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*, 40, 373–383.
27. Ouellette, J. R., Small, D. G. & Termuhlen, P. M. (2004) Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. *Journal of Gastrointestinal Surgery*, 8, 1061–1067.
28. Field, A. (2005) Discovering Statistics Using SPSS. London: SAGE Publications.
29. Ridley, S. (1998) Severity of illness scoring systems and performance appraisal. *Anaesthesia*, 53, 1185–1194.
30. Tsuchiya, M., Suzuki, E., Egawa, K., Nishio, Y., Maegawa, H., Inoue, S., Mitsunami, K., Morikawa, S., Inubushi, T. & Kashiwagi, A. (2004) Stiffness and impaired blood flow in lower-leg arteries are associated with severity of coronary artery calcification among asymptomatic type 2 diabetic patients. *Diabetes Care*, 27, 2409–2415.
31. Enns, R. A., Gagnon, Y. M., Barkun, A. N., Armstrong, D., Gregor, J. C., Fedorak, R. N. & RUGBE Investigators Group (2006) Validation of the rockall scoring system for outcomes from non-variceal upper gastrointestinal bleeding in a Canadian setting. *World Journal of Gastroenterology*, 12, 7779–7785.
32. Howell, S., Coory, M., Martin, J. & Duckett, S. (2009) Using routine inpatient data to identify patients at risk of hospital readmission. *BMC Health Services Research*, 9, 96.
33. Jaeschke, R., Guyatt, G. H. & Sackett, D. L. (1994) Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *Journal of the American Medical Association*, 271, 703–707.
34. McMullan, R., Silke, B., Bennett, K. & Callachand, S. (2004) Resource utilisation, length of hospital stay, and pattern of investigation during acute medical hospital admission. *Postgraduate Medical Journal*, 80, 23–26.
35. de Groot, V., Beckerman, H., Lankhorst, G. J. & Bouter, L. M. (2003) How to measure comorbidity. A critical review of available methods. *Journal of Clinical Epidemiology*, 56, 221–229.
36. Vijan, S. G. (2009) Angiotensin-converting enzyme inhibitors (ACEIs), not angiotensin receptor blockers (ARBs), are preferred and effective mode of therapy in high cardiovascular risk patients. *Journal of the Indian Medical Association*, 107, 178–182.
37. Grothusen, A., Divchev, D., Luchtefeld, M. & Schieffer, B. (2009) Angiotensin II type 1 receptor blockade: high hopes sent back to reality? *Minerva Cardioangiologica*, 57, 773–785.
38. Royal Pharmaceutical Society of Great Britain (2010) British National Formulary (BNF). London: RPS Publishing.
39. British Heart Foundation Statistics Website (2010) Prevalence of all coronary heart disease. Available at: http://www.heartstats.org/datapage.asp?id=1584 (last accessed 13 October 2010).
40. Campbell, S. E., Seymour, D. G., Primrose, W. R. & ACMEPLUS Project (2004) A systematic literature review of factors affecting outcome in older medical patients admitted to hospital. *Age and Ageing*, 33, 110–115.
41. Ruiz, B., Garcia, M., Aguirre, U. & Aguirre, C. (2008) Factors predicting hospital readmissions related to adverse drug reactions. *European Journal of Clinical Pharmacology*, 64, 715–722.
42. Samaras, N., Chevalley, T., Samaras, D. & Gold, G. (2010) Older patients in the emergency department: a review. *Annals of Emergency Medicine*, 56, 261–269.
43. Bottle, A., Aylin, P. & Majeed, A. (2006) Identifying patients at high risk of emergency hospital admissions: a logistic regression analysis. *Journal of the Royal Society of Medicine*, 99, 406–414.
44. Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., Farrar, K., Park, B. K. & Breckenridge, A. M. (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ (Clinical Research Ed.)*, 329, 15–19.
45. Davies, E. C., Green, C. F., Mottram, D. R. & Pirmohamed, M. (2006) Adverse drug reactions in hospital in-patients: a pilot study. *Journal of Clinical Pharmacy and Therapeutics*, 31, 335–341.
46. Bond, C. A., Raehl, C. L. & Franke, T. (2001) Interrelationships among mortality rates, drug costs, total cost of care, and length of stay in United States hospitals: summary and recommendations for clinical pharmacy services and staffing. *Pharmacotherapy*, 21, 129–141.
47. Bond, C. A. & Raehl, C. L. (2008) 2006 national clinical pharmacy services survey: clinical pharmacy services, collaborative drug management, medication errors, and pharmacy technology. *Pharmacotherapy*, 28, 1–13.
48. Bond, C. A., Raehl, C. L. & Franke, T. (2002) Clinical pharmacy services, hospital pharmacy staffing, and medication errors in united states hospitals. *Pharmacotherapy*, 22, 134–147.
49. Bond, C. A. & Raehl, C. L. (2007) Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. *Pharmacotherapy*, 27, 481–493.

