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Association between number of doses per day, number of medications and patient's non-compliance, and frequency of readmissions in a multi-ethnic Asian population

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ABSTRACT

Objective: To investigate whether number of doses per day and number of medications are significantly associated with the number of readmissions and to study the association of readmission frequency with other medical and socio-demographic variables.
Methods: Retrospective cross-sectional study involving 432 patients who were readmitted within 15 days of previous hospital discharge between January 1, 2013 and March 31, 2013. Relevant medical records were collected from the national electronic databases of every public tertiary hospital in Singapore. Significant variables ($p < 0.05$) were identified using forward selection and modeled using generalized linear mixed models.
Results: A total of 649 unplanned readmissions were reviewed. At a multivariable level, number of readmission was significantly associated with the number of medications ($p = 0.002$) and number of doses per day ($p = 0.003$) after adjusting for race, liver disease, schizophrenia and non-compliance.
Conclusion: Complex medication regimen (i.e. multiple medications and multiple doses per day) is a statistically significant predictor of number of readmissions. Simplifying therapeutic regimens with alternatives such as longer-acting or fixed-dose combination drugs may facilitate better patient adherence and reduce costly readmissions.

Introduction

Unplanned readmission is a costly and largely preventable healthcare burden. In their landmark article, Jencks et al. revealed that readmissions account for an estimated USD17.4 billion in annual spending by Medicare (US) (Jencks et al., 2009). Reducing readmission rates has become an imperative among healthcare policymakers. In the United States, the Affordable Care Act authorizes Medicare to impose reimbursement penalties on hospitals for excessive readmissions (Kocher and Adashi, 2011). Causes of readmissions are multi-factorial and many interventions targeted at high-risk patients have been attempted hitherto, albeit with varying degree success (Hansen et al., 2011).

Increased age, multiple comorbidities and polypharmacy, widely defined as the use of five or more drugs, have been identified as contributory factors with the highest risk of readmission Kansagara et al. (2011), Viktil et al. (2007). While age and the presence of comorbidities are unmodifiable, polypharmacy may be addressed via a variety of ways such as medication reconciliation and adoption of judicious prescribing strategies Hanlon et al. (1996). A recent study on medication discontinuation among elderly patients successfully discontinued 311 medications in 64 patients without recurrence or worsening of clinical symptoms. However, as acknowledged by the authors, most of the discontinued medications were clearly inappropriate thus reasonably discontinued (Garfinkel and Mangin, 2010). Such practice may not always be feasible.

Relatedly, the reduction of dosing frequencies, hence number of doses per day, was suggested as an alternative strategy where drug discontinuation may engender adverse outcomes (Garfinkel and Mangin, 2010; Fulton and Riley Allen, 2005). Prescriptions with less frequent dosing regimens have been shown to decrease the occurrence of diseases or symptomatology associated with the drug therapy (i.e. drug-related problems (DRPs)) (Schoonover, 2012; Ingersoll and Cohen, 2008; Strand et al., 1990). However, the association between number of doses per day and readmission frequency remains unclear. The present study investigates the association between number of doses per day and the number of readmissions.

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Methods

Study design

We performed a retrospective, cross-sectional study involving 432 patients who had at least one readmission between January 1, 2013 and March 31, 2013. Institutional review board approval and waiver of consent were obtained from the National Healthcare Group, Singapore.

Patient population

Subjects included patients from a general and acute care hospital in Singapore. Patients who were 18 years and above and readmitted to any public hospital in Singapore within the defined study period were included in the study. Subjects with inaccessible medical records were excluded from the study.

Data collection

All data were collected through the national electronic medical records database, a shared database across all public healthcare institutions in Singapore. Readmission was defined as each unscheduled admission occurring within 15 days of discharge. For patients with multiple readmissions, each episode was counted as a separate readmission.

Details recorded for each readmission included age, sex, race, presence of specific co-morbidities from the Charlson Comorbidity Index (Charlson et al., 1987), number of readmissions, number of medications and number of doses per day dispensed during the previous discharge. Total number of medications included all dispensed medications of different dosage forms or active ingredients. Different dosage forms containing the same active ingredient were counted as separate medications. For instance, a patient using betamethasone cream and betamethasone ointment was considered to have been prescribed two different medications. Different amounts per dosage unit of the same active ingredient in the same dosage form were not counted separately if they were administered with the same dosing frequency. For example, a patient taking one 5 mg enalapril tablet twice daily and one 10 mg enalapril tablet twice daily was considered to be taking only one medication with 2 doses per day.

Number of doses per day referred to the cumulative number of doses for all dispensed medications per day. Doses of medications prescribed on an 'as needed' basis were tabulated based on the maximum number of prescribed doses per day. For example, "two 500 mg paracetamol tablets to be taken orally every 6 hourly as needed" was counted as four doses of paracetamol 1 g per day. Doses prescribed on a non-daily dosing schedule, such as once-weekly dose of alendronate, were recorded as a single daily dose.

All readmission records were reviewed for DRPs diagnosed on admission. Readmission was treated as DRP-related only when it was explicitly stated in the electronic case notes to be caused by a DRP. Documentation of a DRP was based on implicit physician judgment. DRP categories were adapted from those defined by Strand et al. and include patient non-compliance, over-dosage and sub-optimal dosage of the indicated medication and adverse drug reactions (Strand et al., 1990). Non-compliance referred to the failure to adhere to the prescribed drug regimen in terms of doses and dosing schedules (Vermeire et al., 2001).

Statistical analysis

Descriptive statistics was calculated and data was presented as mean ± standard deviation or number and percentage. Univariate regression analyses were performed to identify the prognostic value of each variable in influencing the outcome of number of readmissions in our study population. Variables which were found to be significantly ($p < 0.05$) associated with the outcome variable of number of readmissions in the univariate analysis were subsequently included in a multivariate regression model. Backward elimination was used to simplify the multivariate model, removing variables that had a p value of ≥ 0.05 sequentially, until all remaining variables were significantly associated with the number of readmissions. To account for non-independence and count nature of the dependent variable, generalized linear mixed models (GLMMs) with both Poisson and negative binomial errors were used and compared. Multicollinearity was avoided by ensuring variance inflation factor (VIF) was less than 3 throughout the multivariable regression analyses. All statistical analyses were carried out using the R statistical programing language (version 3.0.1) and GLMMs were fitted using the GLMMadmb package (Fournier et al., 2012).

Results

There were a total of 649 unplanned readmissions during the study period and most (66.6%) were first-time readmissions. The mean age of our sample was 67.7 ± 16.2 years. The mean number of doses per day and number of medications were 18.0 ± 8.0 and 10.0 ± 4.4 respectively. There is a total of 103 DRP-related readmissions, of which non-compliance (5.6%) was the most common iatrogenic cause of readmission. Demographics and clinical characteristics of the readmission events are summarized in Table 1.

Significant univariable correlates ($p < 0.05$) include number of doses per day, number of medications, race not of Chinese, Malay or Indian race (classified as 'other' race), liver disease, anemia and schizophrenia, as shown in Table 2.

There was no difference in results when GLMMs were modeled using Poisson and negative binomial errors. From the GLMM analysis using number of doses per day, factors that significantly increased the number of readmissions in the readmitted population were liver disease ($\beta = 0.33$; $p = 0.002$), diagnosis of schizophrenia ($\beta = 0.44$; $p < 0.001$), documented non-compliance ($\beta = 0.32$; $p = 0.009$), number of doses per day ($\beta = 0.01$; $p = 0.003$) and 'other' race ($\beta = 0.25$; $p = 0.02$), as depicted in Table 3a. When the 'number of doses per day' variable was transformed and expressed in terms of number of medications prescribed, significant variables were likewise, liver disease ($\beta = 0.32$; $p = 0.003$), diagnosis of schizophrenia ($\beta = 0.44$; $p < 0.001$), documented non-compliance ($\beta = 0.32$; $p = 0.009$) and 'other' race ($\beta = 0.25$; $p = 0.02$) and number of medications ($\beta = 0.02$; $p = 0.002$), as seen in Table 3b.

Discussion

We found a significant positive association between number of readmissions and polypharmacy, expressed in terms of number of doses per day and number of medications prescribed. In addition, there was a significant association between non-compliance and the number of readmissions.

Non-compliance is among the most commonly reported iatrogenic causes of readmission (33–69%) (Burke et al., 2000; Steinman, 2007; Claxton et al., 2001). Our study supports this finding, with non-compliance constituting 39 of the 103 DRP-related readmissions. Failure to comply with dosage regimens can lead to suboptimal disease control or rebound symptoms from abrupt cessation, requiring readmissions (Garfinkel and Mangin, 2010). Barriers to medication adherence are largely under the patient's control, with forgetfulness being the most commonly cited (30%) (Osterberg and Blaschke, 2005). Practitioner-led interventions such as regimen simplification are useful in improving compliance (Eisen et al., 1990). Evidence to date suggests that patients adhere more to dosage regimens with fewer medications and in turn are less likely to be hospitalized (Eisen et al., 1990; Col et al., 1990).

Unfortunately, combination therapies are indicated in patients with multiple comorbidities especially if the diseases are poorly controlled (Steinman, 2007; Lipton and Bero, 1992). For instance, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) recommends that 2 or more antihypertensive drugs are required to achieve desired blood pressure levels (James et al.,

Table 1
Demographics and clinical characteristics of events.

Variable	Total number of events (N = 649)
Age (years)	67.7 years ± 16.2
Race	
Chinese	388 (59.8)
Malay	122 (18.8)
Indian	85 (13.1)
Others	54 (8.3)
Gender	
Male	339 (52.2)
Female	310 (47.8)
Number of doses per day	18.0 ± 8.0
Number of medications	10.0 ± 4.4
Co-morbidities	
Diabetes	299 (46.1)
Hypertension	411 (63.3)
Dyslipidemia	331 (51.0)
CHD	213 (32.8)
CVD	87 (13.4)
Hemiplegia	7 (1.1)
CHF	33 (5.1)
COPD	41 (6.3)
Asthma	63 (9.7)
Liver disease	50 (7.7)
CKD	79 (12.2)
Ulcer disease	40 (6.2)
Osteoarthritis	40 (6.2)
Osteoporosis	19 (2.9)
Gout	45 (6.9)
Cataract	39 (6.0)
Anemia	148 (22.8)
Cancer	62 (9.6)
BPH	41 (6.3)
Thyroid	33 (5.1)
Hemorrhoid	2 (0.3)
Epilepsy	29 (4.5)
Dementia	50 (7.7)
Depression	53 (8.2)
Alzheimer's disease	9 (1.4)
Schizophrenia	30 (4.6)
PKD	19 (2.9)
Types of DRPs	
Non-compliance	39 (5.6)
Hypoglycemia	7 (0.9)
Hyponatremia	4 (0.6)
Hypokalemia	4 (0.6)
Metabolic alkalosis	1 (0.2)
Dehydration	7 (0.9)
Low blood pressure	5 (0.6)
Giddiness	5 (0.8)
LFT abnormalities	5 (0.8)
N/V/D	4 (0.6)
Constipation	1 (0.2)
Anemia	2 (0.3)
Thrombocytopenia	4 (0.6)
Rashes	4 (0.6)
Supratherapeutic dose	10 (1.5)
Subtherapeutic dose	1 (0.2)
Number of readmissions	
1	432 (66.6)
2	135 (20.8)
3	46 (7.1)
4	21 (3.2)
5	8 (1.2)
6	5 (0.8)
7	1 (0.2)
8	1 (0.2)

Data shown as mean ± SD or n (%).
Abbreviations: Coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), congestive heart failure (CHF), chronic kidney disease (CKD) benign prostatic hyperplasia (BPH), Parkinson's disease (PKD), drug-related problems (DRPs), liver function test (LFT), nausea, vomiting, diarrhea (N/V/D).

2014). The concurrent administration of multiple antihypertensives may increase patient's risk of severe hypotension necessitating emergency visit and admission (Bangalore et al., 2007). Such a dilemma is not uncommon in other chronic conditions where polypharmacy is necessary for disease control but is associated with undesired outcomes such as readmissions, as seen in our study (Bangalore et al., 2007).

The indispensability of multi-drug therapies underscores the need for alternative approaches to mitigate the heightened risks of non-compliance and readmissions among patients with multiple comorbidities. Reducing the total number of daily doses can effectively encourage patient adherence to their prescribed dosage regimen and

Table 2
Univariable regression with number of readmissions and variables.

Variables	β ($\times 10^{-2}$)	95% CI ($\times 10^{-2}$)	*p* value
Number of doses per day	1.23	0.45, 2.02	0.002
Number of medications	2.55	1.08, 4.02	<0.001
Age	0.029	−0.69, 0.12	0.16
Race[a]			
If malay	−0.04	−17.49, 17.41	1.00
If indian	17.40	−1.66, 36.46	0.07
If others	24.93	2.26, 47.60	0.03
Gender[b]			
If female	−3.00	−16.18, 10.18	0.66
Co-morbidities			
Diabetes	12.84	−0.28, 25.96	0.06
Hypertension	8.44	−5.33, 22.21	0.23
Dyslipidemia	4.25	−8.93, 17.43	0.53
CHD	5.67	−19.87, 8.53	0.43
CVD	−5.33	−24.99, 14.32	0.59
Hemiplegia	17.94	−41.65, 77.54	0.56
CHF	−2.86	−33.15, 27.42	0.85
COPD	9.26	−16.89, 35.42	0.49
Asthma	15.80	−5.35, 36.95	0.14
Liver disease	29.61	7.34, 51.89	0.009
CKD	−1.76	−22.06, 18.55	0.87
Ulcer disease	−24.44	−54.38, 5.50	0.11
Osteoarthritis	7.14	−35.25, 20.98	0.62
Osteoporosis	−7.59	−47.81, 32.63	0.71
Gout	3.85	−22.02, 29.73	0.77
Cataract	9.43	−17.29, 36.15	0.49
Anemia	16.45	1.29, 31.61	0.03
Cancer	−14.57	32.83, 48.35	0.22
BPH	4.57	−22.05, 31.19	0.74
Thyroid disease	−18.57	−50.61, 13.47	0.26
Hemorrhoid	−0.15	−119.72, 119.41	1.00
Epilepsy	2.16	−7.93, 51.26	0.15
Dementia	16.65	−6.80, 40.11	0.16
Depression	13.23	−9.97, 36.42	0.26
Alzheimer's disease	−21.25	−82.93, 40.44	0.5
Schizophrenia	38.75	11.43, 66.07	0.005
PKD	−6.53	−46.66, 33.59	0.75
Non-compliance	25.20	−0.58, 50.91	0.06

Abbreviations: Coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), congestive heart failure (CHF), chronic kidney disease (CKD), benign prostatic hyperplasia (BPH) and Parkinson's disease (PKD).
Reference group:
[a] Chinese.
[b] Male.

Table 3a
Generalized linear mixed model of number of readmissions with number of doses per day.

Variables	β ($\times 10^{-2}$)	95% CI ($\times 10^{-2}$)	*p* value
Number of doses per day	1.14	0.38, 1.90	0.003
Race[a]			
If Malay	0.81	−16.05, 17.67	0.92
If Indian	13.31	−5.12, 31.74	0.16
If others	24.69	3.42, 31.74	0.02
Co-morbidities			
Liver disease	32.72	11.99, 53.44	0.002
Schizophrenia	44.17	19.17, 69.17	<0.001
Drug-related problem[b]			
Non-compliance	31.75	7.94, 55.55	0.009

Reference group:
[a] Chinese.
[b] Absence of drug-related problem.

Table 3b
Generalized linear mixed model of number of readmissions with number of medications.

Variables	β ($\times 10^{-2}$)	95% CI ($\times 10^{-2}$)	*p* value
Number of medications	2.31	0.88, 3.73	0.002
Race[a]			
If Malay	1.67	−15.19, 18.52	0.85
If Indian	13.32	−5.08, 31.75	0.16
If others	24.58	3.33, 45.82	0.02
Co-morbidities			
Liver disease	31.66	10.90, 52.42	0.003
Schizophrenia	43.77	18.81, 68.74	<0.001
Drug-related problem[b]			
Non-compliance	31.75	7.94, 55.56	0.009

Reference group:
[a] Chinese.
[b] Absence of drug-related problem.

improve disease control (Ingersoll and Cohen, 2008; Burke et al., 2000; Claxton et al., 2001). In trials comparing once-daily and once-weekly fluoxetine, patients on once-weekly doses displayed greater adherence rates (Claxton et al., 2000; Delgado, 2000). In a randomized-controlled trial comparing once-daily gliclazide with twice-daily glibenclamide, fasting glucose and HbA1c were better controlled in patients on a once-daily gliclazide regimen (Kardas, 2005).

Despite vast findings on the advantages of reducing number of doses per day, there is no prior evidence on how this intervention will improve hospital readmission rates. From our study findings, readmission frequency is positively correlated with number of doses per day. This suggests that reducing dosing frequency through combination therapies may minimize chances of unplanned readmissions. Undeniably, this strategy is not always applicable, for example, when longer-acting alternatives are unavailable or unsuitable. In these instances, other compliance measures such as constant reminders on the correct use of medications and patient involvement in the pharmaceutical care plan could be utilized (Vermeire et al., 2001).

Readmission disparities among different races have been well-documented among multiethnic populations (Joynt et al., 2011). Among elderly Medicare (US) recipients, African Americans have higher readmission rates compared to Caucasians (Joynt et al., 2011). In comparison, our study found that only the minority race was a significant predictor of readmissions. These racial disparities may be due to an underlying differential socio-economic status among the various races (Russo et al., 2006; Laditka and Laditka, 2006).

Among the comorbidities, liver disease and schizophrenia were significantly associated with readmission at the multivariable level. Liver diseases are complex with many complications such as hepatic encephalopathy, ascites and portal hypertension requiring admission (Berman et al., 2011; Agarwal et al., 1998). For schizophrenia, the patient's lack of insight is a major barrier to adherence and contributor to unplanned readmissions (Agarwal et al., 1998).

Limitations

Unlike most studies listed in the systematic review by Kansagara et al., we used 15-day readmission instead of 30-day readmission as the study outcome (Kansagara et al., 2011). More readmission events would have been recorded had we used the 30-day readmission definition (Goldfield et al., 2008). This could have led to a potential underestimation of the actual number of DRP-related readmissions. Here, the 15-day cut-off was selected because readmissions within 15 days post-discharge was already posing a significant challenge to our healthcare institution, with approximately 6 patients readmitted each day within the defined study period.

As the association between number of doses per day and hospital readmission has never been reported, we conducted a retrospective study to assess the feasibility of a subsequent prospective study. Due to the retrospective study design, the electronic databases used in this study did not contain data on illness severity and social determinants. This is a common issue faced by other studies that relied on retrospective administrative data. In a recent systematic review, only 2 out of a total 32 studies on prediction models of hospital readmission examined the importance of disease severity (Kansagara et al., 2011). Of note, one of the two studies which studied the disease severity found that it was a significant predictor (Burns and Nichols, 1991; Amarasingham et al., 2010). Similarly, the predictive roles of socioeconomic status, education and caregiver availability are poorly studied and remain largely inconclusive (Kansagara et al., 2011). These variables will be considered in a subsequent prospective study.

Conclusion

Readmissions can exert a heavy financial burden on healthcare systems. Though the true proportion of preventable hospital readmissions is not known, unplanned readmissions due to non-compliance can be potentially preventable. In summary, we have demonstrated a positive association between readmission frequency and polypharmacy, as well as non-compliance. Prudent prescribing and the use of longer-acting formulations or fixed-dose combinations might minimize readmissions attributable to non-compliance or polypharmacy, and achieve substantial cost-savings.

Conflict of interest

The authors declare that there are no conflicts of interests.

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