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ORIGINAL ARTICLE

Association between Total Daily Doses with duration of hospitalization among readmitted patients in a multi-ethnic Asian population

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Abstract   Increased length of stay (LOS) in the hospital incurs substantial financial costs on the healthcare system. Multiple factors are associated with LOS. However, few studies have been done to associate the impact of Total Daily Doses (TDD) and LOS. Hence, the aim of this study is to examine the association between patients' LOS upon readmission and their TDD before readmission. A retrospective cross-sectional study of readmission cases occurring from 1st January to 31st March 2013 was conducted at a regional hospital. Demographics and clinical variables were collected using electronic medical databases. Univariable and multiple linear regressions were used. Confounders such as comorbidities and drug related problems (DRP) were controlled for in this study. There were 432 patients and 649 readmissions examined. The average TDD and LOS were 18.04 ± 8.16 and 7.63 days ± 7.08 respectively. In the univariable analysis, variables that were significantly associated with the LOS included age above 75 year-old, race, comorbidity, number of comorbidities, number of medications, TDD and thrombocytopenia as DRPs. In the multiple linear regression, there was a statistically significant association between TDD ($\beta = 0.0733$, $p = 0.030$) and LOS. Variables that were found significant were age above 75 year-old ($\beta = 1.5477$, $p = 0.008$), Malay ($\beta = -1.5123$, $p = 0.033$), other races ($\beta = -2.6174$, $p = 0.007$), depression

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(β = 2.1551, p = 0.031) and thrombocytopenia as a type of DRP (β = 7.5548, p = 0.027). When TDD was replaced with number of medications, number of medications (β = 0.1487, p = 0.021), age of 75 year-old (β = 1.5303, p = 0.009), Malay (β = −1.4687, p = 0.038), race of others (β = −2.6499, p = 0.007), depression (β = 2.1951, p = 0.028) and thrombocytopenia as a type of DRP (β = 7.5260, p = 0.028) were significant. In conclusion, a significant relationship between TDD and number of medications before readmission and the LOS upon readmission was established. This finding highlights the importance of optimizing patients' TDD in the attempt of reducing their LOS.

1. Introduction

Length of stay (LOS) is defined as the number of bed days in each inpatient episode (Berki et al., 1984). It has been identified to be one of the main indicators of hospital performance and patients' consumption of resources (Berki et al., 1984; Becker et al., 1980; Kulinskaya et al., 2005). In Singapore, the mean LOS in the public acute care hospitals is 5.8 days in 2012 (Hospital Services, 2013). Based on the 2012 data, most patients were admitted into the hospital due to accident, poisoning and violence (8.3%), cancer (6.0%) or ischemic heart disease (3.6%) Top 10 Conditions of Hospitalisation, 2014. The national healthcare expenditure constitutes about 4% of Singapore Gross Domestic Product (GDP) in 2013 and is projected to increase as the population ages (Costs and Financing, 2014).

In 2011, healthcare expenditures constituted about 18 percent of the Gross Domestic Product (GDP) in the United States (Pfuntner et al., 2011). As an important variable contributing to cost, increased LOS exerts substantial financial burden on the healthcare system. Extensive studies have also found that reduction in LOS is associated with cost savings. National Health Service (NHS) Institute for Innovation and Improvement in the United Kingdom projected an annual saving of approximately £8 million if the average LOS was shortened by one day (Length of Stay – Reducing Length of Stay, 2008). A study conducted in the United States also showed that with a 1-day and 2-day reduction in LOS, the estimated cost savings could amount to $680 and $1408 respectively (Fine et al., 2000). Reducing LOS will increase the capacity such as inpatient beds and manpower in the healthcare system, improving its productivity and efficiency (Length of Stay – Reducing Length of Stay, 2008). Besides, with an increase in LOS, unplanned rehospitalization and a rise in the adverse drug reactions of all severities could be resulted (Lazarou et al., 1998; Morandi et al., 2013). A 6.1% probability of adverse drug reactions, 20.6% probability of infections and 2.5% probability of ulcers were correlated with a LOS of 8 days 7 nights (Hauck and Zhao, Dec 2011). As patients' LOS increase, patients are exposed to a greater risk of an adverse event (Hauck and Zhao, Dec 2011). LOS therefore, has notable implications on patients' health and the usage of healthcare resources.

While physician and hospital affect LOS, patient characteristics and their medications prior to hospitalization play significant roles in influencing LOS as well (Berki et al., 1984; Lawton and Wholey, 1991; Wuerz and Meador, 1992). A study on the medication use in Singapore nursing homes found that

on average, the residents were on 5.32 medications (Mamun et al., 2004). Patients' extended LOS due to drug related causes are often preventable and their drug related problems (DRPs) can be attributed to polypharmacy (Viktil et al., Feb 2007; Colley and Lucas, 1993). Non-compliance, a commonly cited DRP can be ameliorated through the reduction of pill burden and simplification of regimens (Colley and Lucas, 1993). Although the reduction of pill burden could potentially improve patients' disease control and thereby lead to a reduction in LOS, no direct association has been clearly shown between such an intervention and LOS. Furthermore, previous studies had presented varied responses on the relationship of polypharmacy and LOS (Nobili et al., 2011; Campbell et al., 2004; Incalzi et al., Mar 1992). Studies conducted by Campbell et al. and Incalzi et al. showed that polypharmacy is significantly related to extended LOS (Campbell et al., 2004; Incalzi et al., 1992). On the other hand, Nobili et al. suggested otherwise as polypharmacy was found to be unrelated to LOS in their study (Nobili et al., 2011).

2. Aim of the study

Our study aimed to explore the association between patients' pill burden, more specifically in terms of Total Daily Doses (TDD) and their LOS upon readmission. We hypothesized that higher TDD is associated with longer patient's LOS, potentially due to non-compliance.

3. Methods

3.1. Study design

A retrospective, cross-sectional study was conducted at a regional hospital in Singapore. This study was performed using the electronic medical databases shared by healthcare institutions across Singapore.

Institutional board review and waiver of patients' written informed consent were obtained from the National Healthcare Group, Singapore.

3.2. Subjects

Patients aged above 18 who were first admitted to the regional hospital and subsequently readmitted to any healthcare institutions in Singapore between 1st January and 31st March 2013 were included in this study. Readmission was defined as any unscheduled admission within 15 days of any discharge during the study period.

Patients' baseline demographic characteristics and clinical data were examined through the review of medical records. Demographic data collected were age, gender, race. Patients' race was categorized based on the 3 major ethnic groups in Singapore, namely Chinese, Malay, and Indians. Patients who were not placed into one of these 3 categories were classified as "others". This categorization was important as different ethnic groups had shown significant differences in their health status for the same medical condition (Hughes and Lun, 1990). The classification of comorbidities was taken from Charlson Comorbidity Index (CCI) Charlson et al., 1987.

LOS was defined as the number of days from the first day readmission till the day of discharge. It was numbered sequentially and counted with day 1 being the day of readmission. For example, if the patient was readmitted into the hospital on 10th March 2013 and was discharged on 12th March 2013, the LOS was taken as 3 days.

The number of medications and TDD in this study was defined as the maximum number of medications and doses a patient takes a day. This consisted of acute, chronic, prescription, non-prescription medications, supplements, and those medications that were to be taken when is needed, irrespective of their dosage forms. Medications containing the same active pharmaceutical ingredient but of different dosage forms were considered to be different medications. For example, betamethasone cream and ointment applied by the same patient would be counted as two distinct medications. Different strengths of same medication that had the same dosing frequency on different days were regarded as one medication. Some patients took warfarin 5 mg tablets on certain days of the week and warfarin 3 mg tablets for the remaining days. Warfarin 5 mg and 3 mg tablets here were then counted as one medication only. At the same time, medications such as Alendronate that were taken once weekly were counted as one dose.

The number of medications and TDD was obtained from patients' previous hospital discharge summary. If no medications had been provided in the previous discharge, the number of chronic medications that was dispensed on the nearest date before the previous discharge was taken into account instead.

Patients' DRPs documented in the discharge summary were included in this study. This documentation was done by the clinicians on a voluntary basis and it was based on their clinical judgment. The DRP classification in this was study was adapted from the definitions of Strand et al. (1990). They were further broken down into smaller classifications included hypoglycemia, hyponatremia, constipation, on top of other DRPs such as over dosage and subtherapeutic dosage.

3.3. Analysis

STATA SE version 12.1 for Windows (Stata Corp, College Station, TX) was used in all the statistical analyses.

Descriptive statistics were used to show patient characteristics in the readmission cases collected. Characteristics such as patients' demographics, types of comorbidities, LOS were expressed as mean ± standard deviation or number (percentage).

Univariable linear regression was performed using number of medications, TDD, demographics, types and number of comorbidities and types of DRPs as the independent variables and LOS as the dependent variable. All the variables, irrespective of their p-values and significance, were included in this analysis in order to attain a complete picture of the relationships of LOS with other variables. Earlier studies suggested that patients aged > 75 years were associated with greater risk of hospital readmission and their readmissions were attributed to adverse drug events, hence the age was fixed at 75 year-old in univariable linear regression to examine its association with LOS (Chan et al., 2001; Silverstein et al., 2008).

Statistical significance was defined as $p < 0.05$. Independent variables that exhibited significant relationships in the univariable regression were included in the multivariable linear regression. Multivariable linear regression was performed using LOS as the dependent variable. The number of medications and TDD was used as the independent variables in separate models. The multivariable linear regressions were adjusted with comorbidities and DRPs as they could be confounding factors to the analysis. In this model, being a male, being a Chinese, absence of comorbidities and absence of DRP were the reference categories for gender, race, types of comorbidities and types of DRPs respectively.

To avoid multicollinearity, care was taken to ensure that the variance inflation factor (VIF) to be less than 1 in the analysis.

4. Results

Overall, 432 patients met the eligibility criteria and 649 readmissions were evaluated for this study.

4.1. Baseline characteristics of patients

In the 649 readmission cases collected, patients were aged 67.7 ± 16.2 year-old. Majority of the patients were Chinese (60%, $n = 388$), followed by Malay (19%, $n = 122$) and Indian (13%, $n = 85$). The number of male (52%, $n = 339$) and female (48%, $n = 310$) patients was comparable. Meanwhile, patients involved in readmission had an average of 3.33 ± 1.91 comorbidities. Hypertension, dyslipidemia and diabetes were the main comorbidities, comprising 63% ($n = 411$), 51% ($n = 331$) and 46% ($n = 299$) respectively of the total number of readmissions.

LOS ranged from 1 to 90 days and the mean LOS was 7.63 days ± 7.08. Most of the readmission had a LOS of 2–4 days, making up 36% ($n = 233$) of the total number of readmission events.

On average, the TDD was 18.0 ± 8.2 while the number of medications was 10.0 ± 4.4. The main DRP encountered in this study was non-compliance (6%, $n = 36$). Table 1 showed the summary of the characteristics of readmission events included in the analysis.

4.2. Statistical modeling

In the univariable analysis as shown in Table 2, a significant relationship ($p < 0.05$) was established between LOS during readmission and variables of age (more than 75 year-old), race, comorbidity (hypertension, dyslipidemia, CKD, depression),

Table 1 Characteristics of events.	
Feature	Total number of events ($N = 649$)
Age (years)	67.7 ± 16.2
Race	
Chinese	388 (60)
Malay	122 (19)
Indian	85 (13)
Others	54 (8)
Gender	
Male	339 (52)
Female	310 (48)
Total daily dose	18.0 ± 8.2
Number of medications	10.0 ± 4.4
Number of co-morbidities	3.3 ± 1.9
Types of co-morbidites	
Diabetes	299 (46)
Hypertension	411 (63)
Dyslipidemia	331 (51)
CHD	213 (33)
COPD	41 (6)
Epilepsy	29 (4)
Asthma	63 (10)
CVA	87 (13)
CHF	33 (5)
Liver disease	50 (8)
CKD	79 (12)
Osteoarthritis	40 (6)
Osteoporosis	19 (3)
Gout	45 (7)
Cataract	39 (6)
Dementia	50 (8)
Alzheimer's	9 (1)
Depression	53 (8)
Anemia	148 (23)
Cancer	62 (10)
BPH	41 (6)
Thyroid	33 (5)
Schizophrenia	30 (5)
Hemorrhoid	2 (1)
Hemiplegia	7 (1)
Ulcer disease	40 (6)
PKD	19 (3)
DRPs	
Non-compliance	36 (6)
Hypoglycemia	6 (1)
Hyponatremia	4 (1)
Hypokalemia	4 (1)
Metabolic alkalosis	1 (1)
Dehydration	6 (1)
Low blood pressure	4 (1)
LFT abnormalities	5 (1)
Supratherapeutic dose	10 (2)
Subtherapeutic dose	1 (1)
Rashes	4 (1)
Anemia	2 (1)
Thrombocytopenia	4 (1)
N/V/D	4 (1)
Drowsiness/giddiness	5 (1)
Constipation	1 (1)
Length of stay (LOS)	7.63 ± 7.08

Table 1 (*Continued*)	
Feature	Total number of events ($N = 649$)
1	19 (3)
2	70 (11)
3	76 (12)
4	87 (13)
5	61 (9)
6	57 (9)
7	46 (7)
8	42 (7)
9	37 (6)
10	24 (4)
11	13 (2)
12	20 (3)
13	15 (2)
14	13 (2)
15–19	33 (5)
20–24	18 (3)
25–30	13 (2)
36–90	5 (1)

Data shown as mean $\pm$ SD or n (%).
Abbreviations: Coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD) benign prostatic hyperplasia (BPH), Parkinson's disease (PKD), liver function test (LFT), nausea, vomiting, diarrhea (N/V/D), drug-related problem (DRP).

number of comorbidities, number of medications, TDD and thrombocytopenia as a DRP.

In Table 3, the multiple linear regression that was adjusted with comorbidities and DRP revealed a statistically significant relationship between TDD ($\beta = 0.073$, $p = 0.030$) and LOS. The variables that reached significance included age more than 75 year-old ($\beta = 1.547$, $p = 0.008$), Malay ($\beta = -1.512$, $p = 0.033$), race of others ($\beta = -2.617$, $p = 0.007$), depression as a comorbidity ($\beta = 2.155$, $p = 0.031$) and thrombocytopenia as a type of DRP ($\beta = 7.554$, $p = 0.027$). When TDD was substituted by the number of medications, the same variables remained significant, namely, number of medications ($\beta = 0.148$, $p = 0.021$), age more than 75 year-old ($\beta = 1.530$, $p = 0.009$), Malay ($\beta = -1.468$, $p = 0.038$), race of others ($\beta = -2.6499$, $p = 0.007$), depression as a comorbidity ($\beta = 2.195$, $p = 0.028$) and thrombocytopenia as a type of DRP ($\beta = 7.5260$, $p = 0.028$).

5. Discussion

This study identified that TDD was significantly associated with LOS in both univariable ($\beta = 0.116$, $p = 0.001$) and multiple linear regression ($\beta = 0.073$, $p = 0.030$). Earlier studies found that the number of medications was unassociated with LOS (Nobili et al., 2011; Schuler et al., 2008). However, our results suggested otherwise in both univariable ($\beta = 0.241$, $p < 0.001$) and multiple linear regression ($\beta = 0.148$, $p = 0.021$) as polypharmacy contributed substantially to patients' LOS upon their readmission. This difference may be because we included both prescription and over-the-counter (OTC) medications in our study while earlier studies only took

Table 2 Univariable regression with duration of readmissions and variables.

Variables	Duration of readmissions		
	β (×10⁻²)	95% CI (×10⁻²)	P value
Total daily dose	11.65	5.01, 18.29	0.001
Number of medications	24.14	11.96, 36.33	<0.001
Age (more than 75 year-old)	206.02	94.63, 317.41	<0.001
Race[a]			
If Malay	−215.53	−358.48, −72.57	0.003
If Indian	−175.48	−340.42, −10.54	0.037
If others	−285.96	−486.00, −85.92	0.005
Gender[b]			
If female	150.2	−41.44, 258.95	0.007
Co-morbidities[c]			
Diabetes	−21.59	−131.18, 88.00	0.699
Hypertension	193.13	80.75, 305.51	0.001
Dyslipidemia	110.91	1.95, 219.86	0.046
CHD	20.11	−96.23, 136.46	0.734
CVA	158.98	−0.90, 318.86	0.051
CHF	220.45	−27.65, 468.56	0.081
COPD	137.91	−86.41, 362.23	0.228
Asthma	−159.96	−344.09, 24.16	0.088
Liver disease	−129.46	−334.09, 75.18	0.215
CKD	203	36.65, 369.35	0.017
Osteoarthritis	−67.65	−294.77, 159.47	0.559
Osteoporosis	−22.02	−346.10, 302.06	0.894
Gout	115.65	−99.24, 330.53	0.291
Cataract	30.67	−199.20, 260.54	0.793
Anemia	46.43	−83.73, 176.59	0.484
Cancer	154.5	−30.97, 339.98	1.64
BPH	20.76	−203.81, 245.32	0.856
Thyroid disease	102.33	−146.24, 350.89	0.419
Hem	638.49	−345.96, 1622.93	0.203
Epilepsy	−149.47	−413.65, 114.70	0.267
Dementia	171.75	−32.70, 376.20	0.1
Depression	282.21	83.90, 480.51	0.005
Alzheimer's disease	−154.51	−621.55, 312.52	0.516
Schizophrenia	66.25	−193.90, 326.39	0.617
PKD	173.17	−150.64, 496.97	0.294
Hemiplegia	8.03	−520.88, 5.36.95	0.976
Ulcer disease	−57.00	−284.13, 170.14	0.622
Number of comorbidities	42.50	14.11, 70.88	0.003
Types of DRP[d]			
Non-compliance	138.65	−99.79, 377.10	0.254
Hypoglycemia	−350.05	−920.26, 220.16	0.228
Hyponatremia	−231.63	−1037.40, 574.14	0.573
Hypokalemia	−13.57	−1000.71, 973.58	0.978
Metabolic alkalosis	−163.73	−1556.56, 1229.09	0.818
Dehydration	322.84	−247.47, 893.14	0.267
Low blood pressure	−265.12	−962.88, 432.64	0.456
Giddiness	36.8	−588.04, 661.64	0.908
LFT abnormalities	38.51	−658.70, 735.71	0.914
N/V/D	112.21	−585.80, 810.22	0.752
Constipation	236.88	−1155.88, 1629.65	0.739
Anemia	638.49	−345.96, 1622.93	0.203
Thrombocytopenia	841.71	146.68, 1536.74	0.018
Rashes	−214.81	−912.67, 483.06	0.546
Supratherapeutic dose	296.48	−257.12, 850.08	0.293
Subtherapeutic dose	437.19	−955.29, 1829.67	0.538

Abbreviations: Coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD) benign prostatic hyperplasia (BPH), Parkinson's disease (PKD), liver function test (LFT), nausea, vomiting, diarrhea (N/V/D), not significant (NS); $p > 0.05$, drug-related problem (DRP).

[a] Chinese as reference group.
[b] Male as reference group.
[c] Absence of comorbidities as reference group.
[d] Absence of DRP as reference group.

Table 3 Multiple linear regressions with duration of readmissions and total daily dose or number of medications after adjustments with covariates.

Variables	Duration of readmissions					
	β ($\times 10^{-2}$)	95% CI ($\times 10^{-2}$)	P value	β ($\times 10^{-2}$)	95% CI ($\times 10^{-2}$)	P value
Total daily dose	7.33	0.71, 13.94	0.03	NA	NA	NA
Number of medications	NA	NA	NA	14.87	2.26, 27.47	0.021
Age (more than 75 year-old)	154.77	40.43, 269.11	0.008	153.03	38.67, 267.40	0.009
Race[a]						
If Malay	−151.23	−290.32, −12.13	0.033	−146.87	−285.75, −7.98	0.038
If Indian	−104.62	−270.23, 61.00	0.215	−106.48	−272.02, 59.06	0.207
If others	−261.74	−452.73, −70.74	0.007	−264.99	−455.96, −74.02	0.007
Gender[b]						
If female	91.54	−14.71, 197.78	0.091	89.68	−16.58, 195.94	0.098
Co-morbidities[c]						
HTN	95.15	−27.62, 217.93	0.129	82.5	−41.62, 206.62	0.192
HLD	13.25	−102.44, 128.94	0.822	6.6	−109.57, 122.76	0.911
CKD	161.29	−0.72, 323.30	0.051	157.08	−5.19, 319.35	0.058
Depression	215.51	19.90, 411.12	0.031	219.51	24.16, 414.86	0.028
Types of DRP[d]						
Supratherapeutic dose	292.26	−246.23, 830.74	0.287	268.88	−270.31, 808.07	0.328
Thrombocytopenia	755.48	84.25, 1426.71	0.027	752.6	81.70, 1423.51	0.028

Abbreviations: Drug-related problem (DRP).
[a] Chinese as reference group.
[b] Male as reference group.
[c] Absence of comorbidities as reference group.
[d] Absence of DRP as reference group.

prescription medications into consideration. As the exclusion of OTC medications was suspected to cause the underestimation of the total number of medications taken by the population in other studies, OTC medications were counted to better reflect the actual pill burden of the patients (Bjerrum et al., 1998). In addition to the potential adverse consequences such as DRPs and unintended hospital admissions attributed to OTC medications, there is a high prevalence of concurrent use of both prescription and OTC medications (Eickhoff et al., 2012; Qato et al., 2008). Hence, it was essential to estimate their effects on LOS. This study provided significant insights into the association between pill burden and LOS. To date, the majority of studies on LOS focus on polypharmacy and DRPs, this study was the first to associate the LOS with TDD as well as the number of medications (Nobili et al., 2011; Qato et al., 2008; Gorard, 2006). On top of other implications caused by polypharmacy, this finding would prompt clinicians to use the least possible number of TDDs and medications (Salazar et al., Nov 2007; Fulton and Riley Allen, 2005).

In this study, patients' LOS could be attributed to DRPs caused by high TDD. Due to the nature of a retrospective study, there may be an underestimation of DRPs, causing most of the DRPs to be non-significantly related to LOS. However, as earlier studies had demonstrated that DRPs increase patients' LOS in the hospital, DRPs could still be a plausible link for this association between TDD and LOS in this study (Moura et al., 2009; Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs, 2001).

The multiple linear regressions for the total number of readmissions revealed racial category of Malay and others (encompassed Eurasians, Sinhalese and other minority races) to be significantly associated with LOS. Consistent with the findings from other studies, racial disparity was common in other populations and this had been highlighted (Cook et al., 2006; Hlaing, 2007; de Bruijne et al., 2013). In a European study, researchers found that non-Western ethnic groups had a higher risk for increased LOS as compared to ethnic Dutch patients (de Bruijne et al., 2013). Therefore, clinicians may have to take ethnicity into consideration when examining patients' health outcomes and estimating their LOS.

As mentioned by Uldall et al., there is a significant correlation between psychological comorbidity and LOS (Uldall et al., 1994). In the present study, depression as a comorbidity had a significant relationship with LOS and this was shown in both univariable and multiple linear regressions. This correlation was confirmed by prior studies where psychiatric comorbidity increased patients' average LOS (Uldall et al., 1994; Saravay et al., 1991; Verbosky et al., 1993). Thus, clinicians who are attending to psychiatric patients should be prepared for the possibility of prolonged LOS.

LOS was associated to having thrombocytopenia as a DRP in both univariable and multiple linear regressions. Literatures from the United States and Canada had also documented that patients suffering from thrombocytopenia could have long LOS in the hospital or more specifically the specialized units (Cawley et al., 1999; Crowther et al., 2005). This finding would caution clinicians of the increased risk of prolonged LOS if their patients have DRPs, in particular thrombocytopenia.

5.1. Limitations

Similar to other retrospective studies where important data may not be available, there was an absence of the severity of comorbidities in this study (Hess, 2004). Comorbidities such as hypertension and diabetes that were shown to be associated with patients' LOS in earlier study did not demonstrate significant association (Thombs et al., 2007). Only depression as comorbidity was significantly associated to LOS. Therefore, this study failed to confirm the statistical significance between comorbidities and LOS that were detected by other studies at the multiple linear regression level (Rochon et al., 1996). Similarly, while the complexity and severity of the patients' conditions upon admission were recognized to be a major determining factor of LOS, this information could be not be clearly accounted for in this study (Berki et al., 1984). Notably, this was a common issue seen in risk prediction models for hospital readmissions as limited studies evaluated illness severity (Kansagara et al., 2011).

Besides, the definitions of the different types of DRPs were not standardized. The difference in the definitions of DRPs such as non-compliance could lead to variations in the study outcomes (Cleemput et al., 2002). Without standardized definitions of DRPs, clinicians could have failed to record the possible DRPs. This could potentially lead to an underestimation of the cases related to DRP.

The LOS in this study was taken from the readmissions within 15 days of discharge, while many other studies adopted 30-day readmission (Kansagara et al., 2011). Hence, fewer events were included in this study as compared to other studies on LOS (Nobili et al., 2011; Classen et al., 1997). While Fine et al's study on LOS numbered it by representing the day of admission as day 0, this study numbered the day of admission as day 1 (Fine et al., 2000). As such, the definition of LOS was either unclear or absent in a number of studies on LOS (Nobili et al., 2011; Campbell et al., 2004; Incalzi et al., Mar 1992; Moura et al., 2009; Rochon et al., 1996). Although this deviation and ambiguity in the definition may potentially introduce discrepancies in the results, this difference was assumed to be negligible till other studies prove otherwise.

5.2. Implications

This is the first study to use TDD to investigate the effect of patients' pill burden on their LOS and to establish significant association between TDD and LOS. As far as we know, there had been scant information on the association between number of medications and LOS and there had been no significant associations found (Nobili et al., 2011; Schuler et al., 2008). This study however yielded a significant relationship between numbers of medications and LOS when all the medications (prescription, non-prescription, chronic, acute) were included. Hence, this study introduced a new dimension to the current studies on LOS and polypharmacy as pill burden in terms of TDD was taken into account. TDD is a legitimate concern and important variable to look into. As dosing frequency is known to be one of the main barriers to adherence, less frequent dosing is encouraged (Ingersoll and Cohen, 2008; Haynes et al., 2002; McDonald et al., 2002). This finding would motivate clinicians to take TDD into serious considerations when they prescribe or carry out medical reconciliation.

TDD reduction could be achieved through the use of extended release formulation or combination drugs. This had been reported to minimize patients' risk of taking duplicate medications, enhance their symptomatic control for certain disease states as well as to improve their compliance (Richter et al., 2003; Bae et al., 2012; Paes et al., 1997). TDD reduction and better compliance could translate into reduced healthcare resource utilization and costs (Richter et al., 2003; Toy et al., 2011). However, TDD reduction also presented potential disadvantages. Though these modified products reduce TDD, they were associated with delayed achievement of pharmacodynamics effect and sustained toxicity (Prisant and Elliott, 2003; Ranade, 1991). At the same dosing, the effectiveness of the treatment could be compromised when TDD is reduced. Malo et al. reported that administering budesonide on a four times daily basis instead of twice daily was more effective in controlling asthma, although patients were less compliant and were exposed to more adverse effects (Malo et al., 1995). Certain medications may also be inappropriate for reduced dosing frequency because possible adverse events could be culminated from their pharmacokinetic and pharmacodynamics (Richter et al., 2003).

Future prospective studies are warranted to examine the significance of TDD reduction based interventions on the improvement of patients' LOS. In view of the implications of polypharmacy, it was initially hypothesized in this study that DRP was the cause of the significant relationship between TDD and LOS (Moura et al., 2009; Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs, 2001). Although this study did not show that DRP was the link in the association between TDD and LOS, this introduced a room for future prospective studies with standardized definition of DRPs to confirm this hypothesis.

6. Conclusion

We conclude that TDD before patient's readmission had a significant association with patients' LOS upon readmission. Medication regimen simplification through approaches such as the use the extended release products could be considered to minimize patients' DRP and their LOS.

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