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Original Article

Impact of Potentially Inappropriate Medications on Unplanned Hospitalization among Nursing Home Residents: A Retrospective Cohort Study

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SUMMARY

Background: With the high consumption of medications due to multimorbidity, understanding the quality of drug use for vulnerable nursing home residents is essential. The paper's aim is to investigate the association of potentially inappropriate medication use based on Beers criteria and specific potentially inappropriate medication groups with unplanned hospitalization in nursing home residents.
Methods: This retrospective cohort study consisted of 234 newly admitted consecutive residents aged 65 years and older to one highly accredited nursing home. Cox proportionally hazards regression using stepwise forward method was used to compute hazard ratios and 95% confidence intervals for the association between medication use and time to first hospitalization.
Results: Out of a total of 234 subjects, 56% of the residents had been hospitalized at least once within one year of nursing home admission. Sixty-four percent of the residents were taking at least one potentially inappropriate medication. When accounting for both polypharmacy and potentially inappropriate medication factors, use of two or more potentially inappropriate medications was significantly associated with an increase in hospitalization (HR 2.110, 95% CI 1.358–3.278, p = 0.001). Several combinations of potentially inappropriate medications involving anticholinergic agent were associated with a higher risk of hospitalization in certain subgroups. Further study with a larger representative study sample is warranted to confirm these findings.
Conclusion: Routine medication review for potentially inappropriate medications should be performed for all nursing home resident at admission. Special attention should be paid to residents with use of two or more potentially inappropriate medications due to association with higher hospitalization risk.

1. Introduction

Nursing home (NH) residents are vulnerable to acute illnesses due to advanced age, multiple chronic illnesses, and high levels of dependency.[1] Unplanned hospitalizations are common in this population with more than a quarter of the residents having at least one hospitalization within one year of NH admission,[2–6] and often lead to deterioration in health and even mortality.[7–9]

With the high consumption of medications due to multimorbidity, understanding the quality of drug use for the vulnerable elderly is essential. Among the institutionalized elderly, 44 to 93% were using five or more medications and 21.3 to 65% were using 10 or more medications.[10] Even though most previous studies showed association between polypharmacy and increased hospitalization risk across various NH settings,[11–14] the possibility that polypharmacy was just a mere marker of severe multiple comorbidities could not be excluded.

Potentially inappropriate medication (PIM) had been used as an indicator of drug quality in the elderly. Sets of PIM criteria had been formed and consisted of drugs that may have higher risk of intolerance related to adverse pharmacodynamics or pharmacokinetics in old age. Beers criteria is an explicit list of PIMs best avoided in older adults and is a widely used and well-validated criteria for PIMs.[15,16] PIMs listed in the Beers criteria had been found to be associated with adverse outcomes in the elderly.[17] However, previous studies showed inconsistency in the association between PIM and unplanned hospitalization in NH settings.[14,18–22] Some studies had shown that PIM use was positively associated with hospitalization,[14,20–22] while some had not.[18,19] Moreover, previous studies had focused on the number of PIMs alone, and did not account for the specific PIM groups at the same time.

Our study aimed to investigate the association of PIM use based on Beers criteria and specific PIM groups with unplanned hospitalization in NH residents.

2. Method

This retrospective cohort study consisted of 234 newly admitted consecutive residents aged 65 years and older between the period of January 1st, 2009 to December 31st, 2016 to one hospital-affiliated NH in Northern Taiwan with accreditation of excellence. NHs in Taiwan are evaluated every four years on safety, care quality, administrative, and innovative measures, and graded excellent, very

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good, good, insufficient, and poor accordingly. Since there are currently no unified assessment criteria and care policies for nursing homes in Taiwan, care quality among nursing homes varies widely. By setting aside organizational factors, we hope to focus on the impact of medication quality on unplanned hospitalization in NH residents. All data were collected from patient chart review by one physician.

2.1. Primary outcome measure

The primary outcome measure was unplanned hospitalization after admission to the NH. Some residents experienced more than one hospitalization during the follow-up period, only the occurrence of the first hospitalization was considered for the definition of time-to-event. Time to hospitalization was estimated as the difference between the date of the first hospitalization and the date of NH admission. Those who were not hospitalized, died or moved out within one year of admission to NH were considered censored data.

2.2. Independent variable

Data on medication use at admission was recorded for each resident. We only considered regular prescription medications (those with more than a 28-day supply). Polypharmacy was defined as the use of five or more medications by most studies, and use of 10 or more medications had been termed excessive polypharmacy.[23] Thus, the total number of unique medications were categorized as 0–4, 5–9, and ≥ 10 in our study. PIM use was categorized as 0, 1, ≥ 2, based on Table 2 in the 2015 update to the American Geriatrics Society's Beers criteria.[15] Use of specific PIMs included (1) hypnotic agent, including benzodiazepine (BZD) and non-BZD, was categorized as 0 and ≥ 1, (2) anticholinergic agent was quantified using the anticholinergic risk scale (ARS),[24] and categorized as 0 and ≥ 1, (3) antipsychotic agent was categorized as no use, conventional antipsychotic agent, and atypical antipsychotic agent, (4) nonsteroidal anti-inflammatory drug (NSAID) was categorized as no use, aspirin, and non-aspirin NSAID, and lastly (5) proton-pump inhibitor (PPI) was categorized as no use and use.

2.3. Covariates

We retrieved data at admission for each resident on (1) demographic data: age (categorized as 65–74, 75–84, ≥ 85 y/o) and sex (2) health status: total number of chronic diseases (categorized as 0–1, 2–3, ≥ 4), presence of specific diseases (diabetes mellitus (DM), hypertension (HTN), ischemic stroke, intracranial hemorrhage, Parkinson's disease, dementia, cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), coronary artery disease (CAD), chronic kidney disease (CKD) and patients undergoing hemodialysis), state of consciousness, bedridden status, nutritional status evaluated using short-form Mini-Nutritional Assessment Short-Form (MNA-SF)[25] with 0–7 being malnourished, 8–11 being at risk of malnutrition, 12–14 being normal, (3) functional status: activities of daily living (ADL) score evaluated using Barthel index[26] with 0–20 being totally dependent, 21–60 being severely dependent, 61–100 being mildly to moderately dependent, (4) care-related factors: restraint use, presence of pressure injury, placement of nasogastric catheter, urinary (Foley) catheter, tracheostomy catheter, and transabdominal catheter, (5) do-not-resuscitate (DNR) status, and (6) year of NH admission representing the time variable.

2.4. Statistical analysis

Medication use of the residents, including total number of medications, PIM use, and specific medications, was shown in percentages. Kaplan-Meier analysis was used to determine cumulative percentage of residents hospitalized at one year after NH admission. Cox proportional hazards regression analysis was used to compute hazard ratios and 95% confidence intervals for the association between polypharmacy only (Model 1) and both polypharmacy and PIM variables (Model 2) with time to first hospitalization using the stepwise forward method after inclusion of all the covariates. Interaction terms of the different PIM groups were also included. Sensitivity analyses were performed on residents who had resided for at ≥ 30 days in the NH without any transfer (Model 3) to account for those with relatively more stable medical conditions, as well as on female and male residents separately. SPSS version 24.0 (IBM Corp., Armonk, NY) was used with 5% level of significance.

2.5. Ethical approval

This study was approved by the Mackay Memorial Hospital Institutional Review Board (17MMHIS126).

3. Results

There were 234 subjects in total, with men and women accounting for 37.6% and 62.4%, respectively. Over one-third of our elderly NH population were aged 85 years or older. Almost half of the residents had nearly total dependence, and more than 60% were considered malnourished. About 80% of the residents had at least two or more chronic diseases. The most common chronic disease was HTN (62.4%), followed by DM (44.4%) and ischemic stroke (35%). Sixty percent of residents had placement of at least one indwelling catheter, with nearly 10% having three or more (table not shown).

As for medication use, 82.5% of the residents were taking five or more unique medications at one time, and 20% were taking 10 or more. The mean number of medications per resident was 7.4, with one resident taking up to 19 medications at one time. Cardiovascular medication (83.3%) was the most common category of medication prescribed for the residents, followed by gastrointestinal (76.5%), respiratory (44.9%), and psychiatric medications (35.9%). Those with higher number of medications also had greater number of PIMs (Supplementary Table S1). Over 60% of the residents were taking at least one PIM, with mean number of 1.1 PIM per resident. Commonly prescribed PIMs included hypnotic agents (26.9%), PPIs (26.9%), anticholinergic agents (25.2%), antipsychotic agents (12.0%), non-aspirin NSAIDs (7.6%). Of those using anticholinergic agents, one in three had ARS score greater than or equal to 3 (Supplementary Table S2). A higher percentage of female residents was taking 10 or more medications (22.6% vs. 18.2%). However, male residents were more likely to be taking one or more PIMs (70.5% vs. 61.0%), anticholinergic agents (30.7% vs. 21.2%), atypical antipsychotic agents (10.2% vs. 6.8%), and PPIs (33.0% vs. 23.3%) (table not shown).

Fifty-six percent of the residents had been hospitalized at least once within one year of NH admission. Residents who were hospitalized were more likely to be using higher number of medications and PIMs, and also using PPI (Table 1). In addition, hospitalized residents were of older age, male, in poor state of consciousness, severely dependent, with diagnosis of CHF, CAD, CKD, presence of pressure injury, placement of nasogastric and Foley catheter (Table 2).

Table 1
Medication use of hospitalized nursing home residents.

Medication	Hospitalization rate(%)	Unadjusted HR	p
Total # medication			
0–4	38.2	ref	
5–9	73.8	2.155 (1.175–3.953)	0.013
≥ 10	88.5	3.470 (1.810–6.653)	< 0.001
Total # PIM			
0	62.6	ref	
1	69.6	1.109 (0.717–1.716)	0.642
≥ 2	85.1	1.927 (1.269–2.926)	0.001
Hypnotic agent			
0	71.6	ref	
≥ 1	75.2	0.955 (0.646–1.411)	0.815
Anticholinergic agent			
0	71.1	ref	
≥ 1	76.4	1.422 (0.972–2.080)	0.070
Antipsychotic agent			
No use	71.2	ref	
Conventional	88.9	1.733 (0.845–3.554)	0.133
Atypical	70.5	1.668 (0.919–3.028)	0.093
NSAID			
No use	71.9	ref	
Aspirin	73.0	0.909 (0.530–1.558)	0.727
Non-aspirin	83.3	1.466 (0.643–3.341)	0.363
PPI			
No use	65.3	ref	
Use	87.1	1.886 (1.322–2.690)	< 0.001

NSAID, non-steroidal anti-inflammatory drug; PIM, potentially inappropriate medication; PPI, proton-pump inhibitor.
[1] Use Kaplan-Meier analysis to compute cumulative percentage of residents hospitalized at one year after NH admission.
[2] Use univariate Cox proportional hazards regression analysis to determine unadjusted hazard ratios for association with time to first hospitalization.

Table 2
Characteristics of hospitalized nursing home residents.

	Hospitalization rate (%)	Unadjusted HR	p
Demographics			
Age			
65–74	58.2	ref	
75–84	69.4	1.280 (0.775–2.115)	0.334
≥ 85	82.7	1.829 (1.121–2.983)	0.016
Sex			
Male/female[a]	78.3/68.6	1.533 (1.086–2.162)	0.015
Health status			
Consciousness			
Unclear/clear[a]	86.1/63.1	2.065 (1.467–2.909)	< 0.001
Bedridden			
Yes/no[a]	86.3/54.7	2.316 (1.617–3.315)	< 0.001
Cancer			
Yes/no[a]	81.7/71.1	1.551 (0.962–2.501)	0.072
CHF			
Yes/no[a]	95.8/68.1	2.411 (1.562–3.722)	< 0.001
CAD			
yes/no[a]	86.2/70.5	1.830 (1.136–2.946)	0.013
CKD			
Yes/no[a]	88.6/68.1	1.531 (1.018–2.301)	0.041
Functional status			
ADL			
0–20	87.5	6.744 (2.132–21.327)	0.001
21–60	57.8	2.802 (0.868–9.049)	0.085
61–100	26.9	ref	
Care-related factors			
NG			
Yes/no[a]	84.0/53.1	2.198 (1.520–3.178)	< 0.001
Foley			
Yes/no[a]	86.6/61.2	2.073 (1.472–2.921)	< 0.001
Pressure injury			
Yes/no[a]	84.2/69.8	1.644 (1.077–2.512)	0.021
Restraint			
Yes/no[a]	65.9/74.8	0.801(0.532–1.204)	0.286

[a] reference.
ADL, activity of daily living; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; NG, nasogastric tube.
[1] Use Kaplan-Meier analysis to compute cumulative percentage of residents hospitalized at one year after NH admission.
[2] Use univariate Cox proportional hazards regression analysis to determine unadjusted hazard ratios for association with time to first hospitalization.
[3] Only factors with significant value ($p \leq 0.05$) are shown.

In Model 1 in which we only included polypharmacy as the medication factor, polypharmacy was found to be associated with an increase in risk of hospitalization (5–9 drugs: HR 1.991, p = 0.038; ≥ 10 drugs: HR 3.910, p < 0.001) (Table 3 model 1). However, when we included both polypharmacy and PIM variables in Model 2, use of two or more PIMs was significantly associated with hospitalization (HR 2.110, p = 0.001) (Table 3 model 2).

In addition, age (≥ 85 y/o: HR 2.115, p = 0.005), sex (male: HR 1.687, p = 0.006), cancer (HR 1.822, p = 0.023), CHF (HR 1.912, p = 0.008), undergoing hemodialysis (HR 2.272, p = 0.026), level of dependency (ADL score 0–20: HR 9.020, p < 0.001; ADL score 21–60: HR 4.313, p = 0.017), use of Foley catheter (HR 1.467, p = 0.047) and restraint use (HR 0.618, p = 0.030) all had an impact on hospitalization risk (Table 3 model 2).

In residents who had resided for ≥ 30 days in the NH without any transfer, excessive polypharmacy (≥ 10 medications: HR 3.346, p < 0.001) was associated with hospitalization. In addition, concomitant use of anticholinergic agent and PPI (HR 2.911, p = 0.024) was found to have a higher risk of hospitalization among this group of relatively more stable residents. Other factors associated with hospitalization in this group of residents included age (≥ 85 years: HR 3.498, p = 0.004), state of consciousness (unclear: HR 4.168, p < 0.001), CHF (HR 3.075, p = 0.003), and placement of Foley catheter (HR 2.409, p = 0.003) (Table 3 model 3).

Among male residents, use of two or more PIMs had significantly higher hospitalization risk (HR 2.113, p = 0.025). In female residents, concomitant use of anticholinergic agent with NSAID (HR 6.779, p = 0.003) was associated with a higher risk of hospitalization (Table 4).

4. Discussion

In our study, we found use of two or more PIMs to be associated with increased hospitalization risk. Both polypharmacy and PIM had been used as quality indicators of medication use for the elderly. Our results showed PIM use had a stronger correlation with unplanned hospitalization among our group of NH residents.

Previous studies showed inconsistent results in association between PIM use and hospitalization risk. Residents who received any PIM had greater odds of being hospitalized in the following month than those receiving no PIM in a nationally representative sample of U.S. NH residents (OR 1.27).[27] Ruggiero et al. found Italian NH residents with two or more PIMs at baseline had a higher probability of being hospitalized (HR 1.73) during the following 12 months.[22] However, PIM exposure was not associated with adverse outcomes including hospitalization in a multicenter study in Japan.[19] In our study, we also used Beers criteria, which was a well-validated tool that allowed easy comparison with the other studies,[28] and found exposure to two or more PIMs to have higher risk for hospitalization.

Table 3
Factors associated with hospitalization among nursing home residents.

	Model 1 (n = 230)		Model 2 (n = 230)		Model 3 (n = 132)	
	HR	p	HR	p	HR	p
Medication						
Polypharmacy (ref: 0–4)						
5–9	1.991	0.038	-	-	-	-
≥ 10	3.910	< 0.001	-	-	3.346	< 0.001
PIM (ref: 0)						
1	-	-	1.004	0.987	-	-
≥ 2	-	-	2.110	0.001	-	-
Anticholinergic*PPI (ref: no use)						
Concomitant	-	-	-	-	2.911	0.024
Demographics						
Age (ref: 65–74)						
75–84	1.268	0.368	1.353	0.256	1.327	0.493
≥ 85	1.800	0.023	2.115	0.005	3.498	0.004
Sex (ref: female)						
Male	1.528	0.027	1.687	0.006	1.610	0.120
Health status						
Consciousness (ref: clear)						
Unclear	2.055	0.004	-	-	4.168	< 0.001
Cancer (ref: no)						
Yes	2.125	0.006	1.822	0.023	-	-
CHF (ref: no)						
Yes	1.956	0.009	1.912	0.008	3.075	0.003
CAD (ref: no)						
Yes	1.781	0.026	-	-	-	-
Hemodialysis						
Yes	-	-	2.272	0.026	-	-
Functional status						
ADL (ref: 61–100)						
0–20	4.846	0.011	9.020	< 0.001	-	-
21–60	3.579	0.036	4.313	0.017	-	-
Care-related factors						
Foley						
Yes	-	-	1.467	0.047	2.409	0.003
Restraint (ref: no)						
Yes	0.481	0.002	0.618	0.030	-	-

ADL, activity of daily living; CAD, coronary artery disease; CHF, chronic heart failure; PIM, potentially inappropriate medication; PPI, proton-pump inhibitor.
[1] Model 1: Use multivariate Cox regression analysis (stepwise forward method) and included demographic, health, functional, care-related factors and polypharmacy.
[2] Model 2 (all residents) & Model 3 (residents with at least 30-day NH stay without transfer): Use multivariate Cox regression analysis (stepwise forward method) and included demographic, health, functional, care-related factors, and all medication factors (including polypharmacy and PIMs).

Table 4
Factors associated with hospitalization among nursing home residents according to sex.

	Female (n = 142)		Male (n = 87)	
	HR	p	HR	p
Medication				
PIM (ref: 0)				
1			0.835	0.608
≥ 2			2.113	0.025
Anticholinergic*NSAID (ref: no use)				
Non-aspirin	6.779	0.003		
Aspirin	1.871	0.546		
Demographics				
Age(ref: 65–74)				
75–84	2.466	0.041	1.021	0.951
≥ 85	3.750	0.002	1.958	0.073
Health status				
Cancer (ref: no)				
Yes	5.511	< 0.001		
CHF(ref: no)				
Yes	3.001	< 0.001		
Functional status				
ADL (ref: 21–100)				
0–20	3.235	< 0.001	2.057	0.013

ADL, activity of daily living; CAD, coronary artery disease; CHF, chronic heart failure; NSAID, non-steroidal anti-inflammatory drug; PIM, potentially inappropriate medication.
[1] Use multivariate Cox regression analysis (stepwise forward method), including demographic, health, functional, care-related factors, and all medication factor (including polypharmacy and PIMs).

Most previous literature had shown positive association between polypharmacy and hospitalization in the NH population.[11–13] However, the high number of drug use could be expected in elderly patients due to increase in comorbidities. Initially, our results showed polypharmacy was associated with increased hospitalization risk (Table 3 model 1), but this association was not found after also accounting for PIM variables (Table 3 model 2). Among NH residents who resided for ≥ 30 days without transfer, excessive polypharmacy was found to be correlated with hospitalization but PIM use was not (Table 3 model 3). Our finding might have implied the greater impact of PIM on hospitalization during the first month of NH admission. However, the results should be interpreted with caution since we only accounted for the medications prescribed at NH admission.

Our study found several combinations of PIMs involving anticholinergic agents to be associated with higher risk of hospitalization in our NH population. The use of anticholinergic agent was associated with higher risk of hospitalization when combined with non-aspirin NSAIDs in the female group and with PPI in the more stable subgroup. Anticholinergic agents and NSAIDs had been well-known for their deleterious effect on elderly patients.[29,30] Chronic PPI use had also been found to have potential risk for various clinical outcomes including gastric atrophy, osteoporosis, dementia, pneumonia, renal injury, falls.[31,32] According to the 2015 Beers criteria, PPIs should be generally avoided for greater than 8 weeks of use. However, since the National Health Insurance in Taiwan provided cover-

age for 16 weeks of PPI use when clinically indicated, patients were commonly treated with greater than 8 weeks of PPI regardless of age. This might explain the high percentage of PPI users among our NH population. Our result also implied possible harmful effects from long-term PPI use. In addition, main reasons for hospitalization in our group of NH residents were due to infectious diseases, including pneumonia and urinary tract infection, and gastrointestinal bleeding.

Residents of older age (≥ 85 years) and male sex were more likely to be hospitalized in our NH population. Among the relatively more stable residents, we still found residents ≥ 85 years of age at an increased risk for hospitalization, but the role of gender diminished. A 2016 review concluded the influence of age was less clearon hospitalization in NH residents.[33] The review pointed out that the inconsistent findings on the influence of age may be due to the fact that age was mostly assessed as a linear variable or with only few categories in most studies. We categorized the residents in our study into three age groups, 65–74 y/o, 75–84 y/o and ≥ 85 to be able to distinguish between the subtle differences among the elderly population. Previous literature had shown male NH residents at higher risk for hospitalization.[33] We found use of two or more PIM to be associated with unplanned hospitalizations in our group of male residents. This association deserved investigation in further studies with larger sample sizes. In addition, residents with diagnosis of CHF and placement of Foley catheter were associated with higher hospitalization risk. This still held true in the more stable subgroup of residents. These findings were compatible with earlier studies which showed these two groups of patients to be more susceptible to hospitalization.[3,34]

There were several limitations to our study. First, study subjects were only from one institution in Taiwan. Nevertheless, we chose a highly accredited NH in Northern Taiwan in which nursing care was above standards and wished to focus on medication factors and their impact on unplanned hospitalization in NH residents. Second, study subjects were from one hospital-affiliated NH, which might influence the healthcare utilization pattern of the residents. Third, we did not account for short-term or as-needed prescription medications and use of non-prescription medications. Short-term medications were usually intended for treatment of acute conditions and used for a limited period of time, e.g. usually less than a week. The most common non-prescription medication used by the residents in our study were multivitamin supplements. Fourth, we used baseline data for medication use as well as other variables, so we were unable to account for the differences over the course of time. Lastly, some residual confounding factors still might exist in this study, for example, objective measure of the subject's physical function.

Our study found NH residents using two or more PIMs listed in the Beers criteria to have higher risk for hospitalization. In addition, combinations of PIMs that included anticholinergic agents were associated with an increase in hospitalization among certain subgroups. The use of anticholinergic agent was associated with a higher risk of hospitalization when combined with NSAID and PPI in the female residents and the relatively more stable residents, respectively. Further research with a larger study sample is warranted to determine the impact of the different PIMs on hospitalization risk in the NH population.

5. Conclusions and implications

Routine medication review for PIMs should be performed for all NH residents at admission. Special attention should be paid to NH residents with two or more PIMs in their medication list due to an association with higher hospitalization risk. Furthermore, a unified assessment criteria that included PIM screening should be implemented in nursing homes in Taiwan to better understand and improve quality of care for these residents.

Declarations

We certify that all our affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties).

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Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=23.

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