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Associations of potentially inappropriate medication use with four year survival of an inception cohort of nursing home residents

Running title: Associations of PIM use with survival

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Highlights:

- 36% of nursing home residents were still alive after 4 years
- Polypharmacy and PIM use were high
- People with dementia and high care dependency died earlier
- No association between polypharmacy or PIM use and survival

Abstract

Background: Survival in older adults has a high variability. The possible association of length of survival with potentially inappropriate medication (PIM) use remains unclear.

Aim: to examine the four-year survival rate, the prevalence of polypharmacy and PIM use at admission, and the association between the two, in an inception cohort of newly admitted nursing home residents

Methods: Data were used from ageing@NH, a prospective observational cohort study in nursing homes. Residents (n=613) were followed for four years after admission or until death. PIM use was measured at admission, using STOPPFrail. The Kaplan-Meier method was used to estimate survival, using log-rank tests for subgroup analyses. Cox regression analyses was used to explore associations with PIM use and polypharmacy, corrected for covariates

Results: Mean age was 84, 65% were females. After one, two, three and four years the survival rates were respectively 79%, 60.5%, 47% and 36%. At admission, 47% had polypharmacy and 40% excessive polypharmacy, 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs. No difference in survival was found between polypharmacy and no polypharmacy, and PIM use and no PIM use at admission. Neither polypharmacy nor PIM use at admission were associated with mortality.

Conclusion: Residents survived a relatively short time after NH admission. Polypharmacy and PIM use at admission were relatively high in this cohort, although neither was associated with mortality.

Key words: survival analyses, dementia, polypharmacy, potentially inappropriate medications, nursing home

1. Introduction

Survival in older adults differs in length, and has been associated with different factors, such as multimorbidity, physical and cognitive decline, and frailty (Huang et al., 2017; Kamo et al., 2017; Koroukian et al., 2016; Rizzuto et al., 2017). The association of polypharmacy and potentially inappropriate medication (PIM) use with mortality is also debated. Previous studies on this item have concentrated at one time point, but the association of polypharmacy and PIM use with the longitudinal evolution of survival remains unclear (Bo et al., 2018; Muhlack et al., 2017; Schlesinger et al., 2016). This study focusses on four year survival and its association with polypharmacy and PIM use according to the STOPPFrail criteria (Screening Tool of Older Persons Prescriptions in Frail older adults with limited life-expectancy) (Lavan et al., 2017). The study population is an inception cohort

of newly admitted nursing home (NH) residents: a group of older adults, included after their first admission in a NH, and followed thereafter .

Generally, NH residents are a frail population with a high prevalence of multimorbidy, high care dependency, and dementia (Holmes and Sachs, 2017; Kojima, 2015). Furthermore, multimorbidity is commonly treated with high levels of medications and also PIMs (Davies and O'Mahony, 2015; Lavan et al., 2017; Vetrano et al., 2013). PIM use has been studied extensively in older adults with a normal life-expectancy. Numerous implicit (e.g. MAI (Samsa et al., 1994)) and explicit tools (e.g. STOPP/START (O'Mahony et al., 2015)) have been developed to guide clinicians with discontinuation of these PIMs. Depending on the tool used, between 24% and 95% of NH residents are exposed to PIMs (Morin et al., 2016; Sevilla-Sanchez et al., 2017). PIM use has been associated with adverse outcomes such as falls, adverse drug events, hospitalizations and mortality in older adults with a normal life expectancy (Fried et al., 2014). However, these tools do not take the frailty and limited life-expectancy of most NH residents into account. Only recently, specific – STOPPFrail – criteria were developed for this population (Lavan et al., 2017).

The main care goal in a frail population with limited life-expectancy should be preservation of quality of life. In this context, it is crucial to prevent negative medication-related outcomes, i.e. by identifying and discontinuing PIMs. Furthermore, to ensure appropriate care by NH staff with expertise regarding the areas of care that are most needed, it is vital to get an insight in the average survival time after NH admission, and its associated factors. This information is also important for policy makers and NH managers to estimate future long-term care needs and the related costs, and to determine the policy regarding waiting lists.

The aim of this study is to examine, in an inception cohort of newly admitted NH residents, the four-year survival rate, the prevalence of polypharmacy and PIM use according to the STOPPFrail criteria at NH admission, and the association between the two, corrected for covariates.

2. Materials and methods

This study uses data of the ageing@NH cohort study, examining the general health of NH residents at admission and during their four-year stay in the NH or stay until death. Two other articles reporting on data of this study were published earlier (Ivanova et al., 2018; Paque et al., 2017). More information on methods can be found there.

2.1 Study design and study population

A convenience sample of 67 NHs in Flanders, the Dutch speaking part of Belgium, were included in the study. In the participating NHs, all newly admitted residents between September 2013 and December 2013 were invited to participate in the study, if aged >= 65, Dutch-speaking and permanently admitted to the NH. All residents were consecutively recruited during the period of four months for the baseline assessment at NH admission. All residents - or their proxy decision maker in case of dementia - had to provide informed consent.

2.2 Procedure

Residents were interviewed one to three months after admission using a structured questionnaire and validated measuring tools for activities of daily living (Katz-ADL) (Katz et al., 1963) and mental health (MMSE) (Cockrell and Folstein, 1988) *(supplementary: appendix 1)*. These baseline data were completed with administrative data (date of birth, admission and date of death), data from the nursing chart, and a copy of the resident's medication chart. In case of dementia, the proxy decision maker was interviewed.

Survival data (alive or death, date of death) were collected during four years after study entry. A follow-up assessment was conducted one and two years after NH admission, but these data were not included in our analyses. We focused on the assessment at NH admission because one of the main aims was to examine if polypharmacy and PIM use at admission were associated with the survival rate after admission.

2.3 Data handling

Medication use was based on a copy of the full medication chart. Medications were recorded using the brand or generic name in a data-entry program, based on the official register of medications on

the market from the Belgian Centre for Pharmaceutical Information. The medication was translated into the Anatomical Therapeutic Chemical (ATC) classification (WHO ATC/DDD index). Polypharmacy was defined as the use of five or more prescribed chronic medications, and extreme polypharmacy as the use of ten or more. The prevalence of PIMs was measured using the STOPPFrail criteria (Lavan et al., 2017). STOPPFrail is a list of explicit criteria for PIM use, aiming to assist clinicians with deprescribing medications in frail older adults with limited life-expectancy in all healthcare settings. This list was created based on the authors' clinical experience in geriatric pharmacotherapy and literature appraisal. The draft criteria were distributed to a panel of experts for validation by the Delphi technique (Lavan et al., 2017). The STOPPFrail criteria were cross-referenced and linked to the baseline medications. Because the clinical information necessary to interpret their [in]appropriate use was not available in this study, we excluded, based on experts' opinions (RVS and TC), the following medications: anti-platelets, leukotriene antagonists, muscarinic antagonists, diabetic oral agents, ACE inhibitors, angiotensin receptor blockers, and prophylactic antibiotics.

High care dependency was defined as a KATZ-ADL score greater than 17, based on the highest tertile of the frequency distribution at baseline. Residents with an MMSE score lower than 16 out of 30, and a KATZ score for disorientation greater than or equal to 6 out of 8 – showing a daily disorientation in time and place – and who were unable to respond adequately to the questionnaire, were considered to have dementia symptoms. People without dementia, who were living alone before admission and not being directly transferred from hospital to the NH, were considered as social admittance.

2.4 Data analysis

All statistical analyses was done using SPSS 23.0 (IBM Statistics Inc., Chicago, IL). Resident characteristics were explored with descriptive statistics. The Kaplan-Meier method was used to estimate survival, using 31/12/2017 as the censor date for the survivors, and using log-rank tests for subgroup analyses. Residents who moved during the observation period (e.g. to another NH) were excluded from further analyses. A Cox proportional hazards model was developed to examine

associations of polypharmacy, PIM use and covariates with mortality. A statistical significance level of $p < 0.05$ was set.

2.5 Ethical considerations

The study protocol was approved by the ethics committee of the Antwerp University Hospital Belgium (EC-number 13/43/420).

The board of directors and the supervising general practitioner (GP) of the NH signed a study agreement. Residents or their legal representative signed an informed consent.

3. Results

3.1 Study population

At NH admission, mean age was 84 years, and 65% were females (n=613). The most important reasons for NH admission were physical decline (63%) and increasing care needs (58.5%), followed by cognitive decline (36%), and social admittance (24%). Mean Katz-ADL was 15.6 (range 6-24), 38% were highly care dependent, and 34% had dementia symptoms.

(Table 1).

3.2 Survival rates over four years

Mean survival time after admission was 31 months. One year after NH admission, 79% was still alive. The cumulative survival rates after two, three and four years were respectively 60.5%, 47%, and 36%, with every year a decrease of the yearly mortality.

(Figure 1.).

3.3 Medication use and PIM use according to STOPPFrail at NH admission

At admission, participants used a mean of 9 medications, 47% had polypharmacy (5-9 chronic medications), and 40% excessive polypharmacy (>= 10 chronic medications). Mean number of PIMs was two (range 0-6), 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs according to the STOPPFrail criteria. The most commonly used PIMs were

proton pump inhibitors (PPIs) and H2 receptor antagonists (41%), vitamins (32%), antipsychotics (28%), calcium (28%), and lipid modifying agents (26%).

(Table 2).

3.4 Associations of four year survival

3.4.1 With polypharmacy and PIM use: Survival analyses with Kaplan Meier showed no difference in survival between no polypharmacy, polypharmacy and excessive polypharmacy at admission, neither between PIM use and no PIM use at admission (data not shown). No associations were found between polypharmacy and mortality, and between PIM use and mortality in Cox regression analyses (resp. p=0.150, p=0.901). (Figure 2.) (Table 3.)

3.4.2 With covariates: Survival rates were lower in residents with high care dependency and dementia symptoms compared to residents who were less care dependent and without dementia symptoms (both p<0.001). (Figure 1.). Survivors were more hospitalized during the year before admission compared to the deceased (p=0.011) (Table 3.). In addition, a higher survival rate was associated with social admittance, younger age and female gender (p=0.036, p<0.001 and p=0.029 respectively). (Figure 1.) (Table 3).

4. Discussion

4.1 Main Findings

One year after NH admission, 79% of the residents were still alive. Only 36% survived for four years. At admission, 47% had polypharmacy and 40% excessive polypharmacy. According to the STOPPFrail criteria, 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs. Survival did not differ between residents with or without polypharmacy, nor between those who used PIMs and those who did not. Neither polypharmacy nor PIM use were associated with mortality.

4.2 Strenghts and limitations

To the best of our knowledge, this is the first study exploring survival in a large inception cohort of NH residents, who were included in the study at NH admission, and followed for four years. This study provided extensive data on the general health and medication use of the study population, enabling us to explore associations of medication use and covariates with survival, which are highlighted in Kaplan Meier analyses.

A few limitations apply to this study. Firstly, PIM use is not registered in Flemish NHs. Consequently, the STOPPFrail criteria were applied to all medications on the resident's medication chart, and only PIMs for which clinical information is not necessary to determine whether their use is inappropriate or not, could be identified. Thus, the high prevalence of PIM use in this study is an underestimation. Furthermore, this limitation can at least partly explain the null result regarding the associations of polypharmacy and PIM use with mortality. Secondly, unmeasured confounders such as comorbidities and omission of potentially beneficial medications may have caused bias. Research has demonstrated the negative effects of both confounders on survival in older adults (Rizzuto et al., 2017; Wauters et al., 2016). Thirdly, the absence of clinical information limited our findings regarding physical health to activities of daily living measured with the KATZ-ADL, which is mandatory in Flanders. Furthermore, we determined dementia symptoms based on screening of cognitive impairment and resident ability to respond to the questionnaire and not on diagnosis. However, research has demonstrated that cognitive impairment is relevant to predict long-term mortality (Lee et al., 2009). Finally, only medication data at NH admission were used. Polypharmacy and PIM use during follow-up may have changed due to changes in health status or disease burden, but these changes were not taken into account.

4.3 Interpretations of the findings

We found that less than 50% of newly admitted residents survived longer than three years after NH admission. This was concordant with the findings of a large-scale study of three-year mortality of newly admitted NH residents in Iceland (Hjaltadottir et al., 2011). However, survival rates may vary

among studies in countries with a different healthcare system and different criteria for NH admission. In Flanders extensive home care facilities are available. Thus, NHs provide care for older adults with multimorbidity and serious functional disabilities – ADL and/or cognitive impairment – and increasing care needs that cannot be met in any other way. This is reflected in this study by the most important reasons for admission – physical and cognitive decline, and increasing care needs – and the high prevalence of dementia symptoms and high care dependency at admission. Concordant with earlier research, these findings support the assertion that, generally, older adults or older and frailer at NH admission, and their health has deteriorated to an extend that long-term survival becomes exceptional (Hjaltadottir et al., 2011; Lee et al., 2009; Schlesinger et al., 2016; Sund Levander et al., 2016).

We found a high prevalence of polypharmacy and PIM use at admission according to STOPPFrail. Comparison with other studies on PIM use in NHs is difficult because the prevalence of PIMs depends on the method and the tool used. Moreover, the STOPPFrail criteria were published only recently and we found no other studies in NHs using these criteria to measure PIM use.

Surprisingly, and notwithstanding polypharmacy and PIM use are generally considered to be a big problem in frail older adults because of the associated negative health outcomes (Fried et al., 2014; Muhlack et al., 2017), we found no association of polypharmacy and PIM use with long-term survival or mortality. Other studies in NH residents, and in community dwelling and hospitalized older adults on these associations are inconsistent (Franchi et al., 2016; Schlesinger et al., 2016; Wauters et al., 2016). Muhlack et al. found that the intake of PIMs was associated with increased mortality, but only if prevalent users were excluded from the analyses and a new-user study design was applied (Muhlack et al., 2017). In the current study, participants were taking PIMs at NH admission, and in most cases they had probably been taking them for some time before their admission. The treating physician in Flemish NHs is usually the resident's former family physician, which supports the assumption that the same medications were used before and after admission and changes to the

medication chart had not been made yet at the time of data collection. Thus, residents using PIMs at admission can be considered as prevalent users who probably tolerate their medication, and benefit from it, which increased the risk of healthy-user / sick-stopper bias and may partly explain the null results (Muhlack et al., 2017). Additionally, the before mentioned limitations of our study regarding the underestimation of PIM use due to the limited applicability of the STOPPFrail criteria and unmeasured confounders are possible explanations for the null results. In this context, Wauters et al found an increased risk of mortality for every additional underused medication that was clearly indicated and likely to benefit the patient in community dwelling older adults, while associations with misuse were less clear (Wauters et al., 2016). Finally, other outcomes might be more relevant for polypharmacy and PIM use than mortality (e.g. quality of life, adverse drug reactions, falls) (Fried et al., 2014; Schlesinger et al., 2016).

4.4 Implications for practice

Our findings on the relatively short survival after NH admission highlight the importance of a palliative approach in NHs. Hence, NH staff should be trained in providing palliative care for these residents, and focus on supporting and preserving quality of life, in accordance with the resident's wishes and preferences. In this context, initiation of advance care planning (ACP) shortly after NH admission is crucial. Furthermore, ACP should be embedded into routine care, involving the resident and his family, and targeting different aspects of care and treatment, e.g. discontinuation or deprescribing of PIMs. The absence of an association of polypharmacy and PIM use with mortality raises the question if polypharmacy and PIM use have a crucial role in NH residents' mortality, a population with such a high multimorbidity. Probably mortality is not the best outcome measure in this context. Further research should focus on associations with more subtle outcomes such as quality of life and side-effects, taking into account comorbidities and underuse of beneficial medications. Nevertheless, prescribers should always weigh the benefits and risks at the individual level when prescribing medications.

4.5 Conclusion

One year after NH admission, 79% of the residents were still alive. Only 36% survived for four years. At admission, polypharmacy and PIM use were relatively high. Survival did not differ between residents with or without polypharmacy, nor between those who used PIMs and those who did not. Neither polypharmacy nor PIM use at admission were associated with mortality.

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Declarations of interest: none

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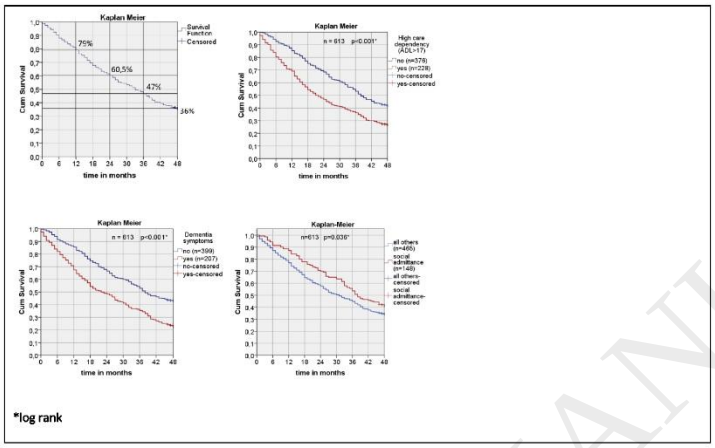
Figure 1. Survival rates of an inception cohort of newly admitted NH residents and differences in long-term survival according to level of ADL dependency, presence of dementia symptoms and social admittance

Figure 1. Survival rates of an inception cohort of newly admitted NH residents and differences in long-term survival according to level of ADL dependency, presence of dementia symptoms and social admittance



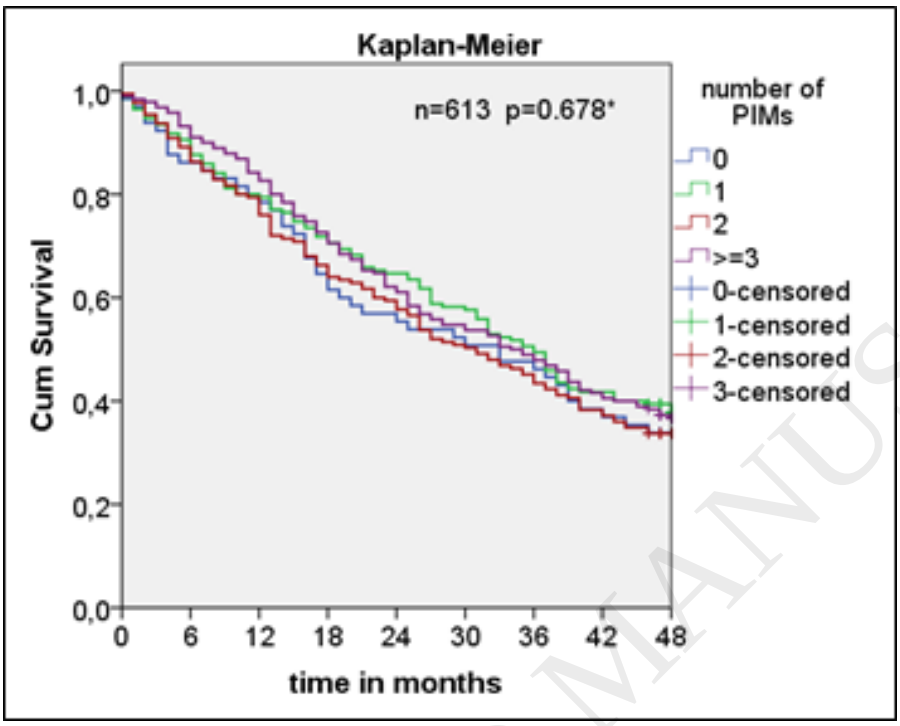
Top left: **cumulative survival of newly admitted NH residents**: at admission (month 0) everyone is still alive, 12 months after NH admission 79% is still alive, and after 24, 36 and 48 months resp. 60.5%, 47%, and 36% are still alive.

Top right: **Difference in survival between residents with high (ADL>17) and lower care dependency**: residents with high care dependency die sooner compared to those with lower care dependency

Bottom left: **Difference in survival between residents with and without dementia**: residents with dementia die sooner than residents without dementia

Bottom right: **Difference in survival between social admittance and all others**: residents without dementia, living alone before NH admission, and not transferred directly from hospital to the NH live longer compared to the others

Figure 2. Differences in long-term survival according to the number of PIMs used



*log rank

No differences in survival were found between residents taking no PIMs and residents taking one, two, and three or more PIMs

Table 1. Basic characteristics of the study population

	All **n=613**
Age in yrs mean (SD) **(range)**	84.02 (6.63) (65-105)
Gender (%): **female** **male**	 65.4 34.6
Survival in months mean (SD) **(range)**	30.81(17.33) (0-48)
Total medication mean (SD)	8.94 (3.92)
Polypharmacy (%): **No polypharmacy (0-4)** **Polypharmacy (5-9)** **Excessive polypharmacy (>= 10)**	 12.3 47.4 40.3
Most important reason for admission* (%): **physical decline** **increasing care needs** **cognitive decline** **increasing caregiver burden** **other**	 62.6 58.5 36.1 16.5 24.0
Living situation before admission (%): **alone** **with partner, partner and children or children** **other**	 61.6 35.6 2.8

Stay before admission (%):	
hospital	42.9
at home	21.7
other	35.4
Social admittance (%)	24.1
Hospitalization year before admission (%)	68.9
Katz ADL mean (range 6-24)	15.63
High care dependency (ADL>17) (%)	37.7
MMSE mean (range 0-30)	18.40
Dementia symptoms (%)	34.2

**more than one answer possible*

Table 2. Prevalence of Potentially Inappropriate Medications (PIMs) in frail older adults with limited life-expectancy according to the STOPPFrail criteria (Lavan et al., 2017)

PIM use at admission	**n=613**
Number of PIMs mean (SD)	1.94 (1.201)
(range)	(0-6)
Prevalence of PIM use (%):	
no PIMs	10.6
1 PIM	28.2
2 PIMs	29.4
>= 3 PIMs	31.8
STOPPFrail criteria (%):	
PPIs and H2 receptor antagonists	40.8
multi-vitamin combination supplements	31.6
neuroleptic antipsychotics	28.0
calcium supplements	27.7
lipid modifying agents	26.3
anti-dementia (incl. memantine)	15.0
5-alpha reductase inhibitors	10.3
long-term oral steroids	4.1
anti-hypertensives (incl. alpha blockers)	3.9
long-term oral NSAIDs	3.8
sex hormones (including SERMS)	2.4

Table 3. Mortality and associated characteristics at NH admission, Cox regression

Mortality (n=613)	**4-year survivors n=219**	**Deceased n=394**	**p-value***	**Unadjusted HR(95%CI)**
Number of PIMs mean	1.94	1.95	0.901	0.99(0.92-1.04)
PIM use (%):			0.682	
0 PIM (reference category)	10.0	10.9		1
1 PIM	30.6	26.9		1.12(0.79-1.59)
2 PIMs	26.9	30.7		0.98(0.76-1.28)
>= 3 PIMs	32.4	31.5		1.13(0.87-1.45)
Total medication mean	8.98	8.92	0.855	1.00(0.98-1.03)
Polypharmacy (>5) (%)	85.4	89.3	0.150	1.34(0.97-1.85)
High care dependency (%) (ADL>17)	27.2	40.0	**<0.001**	1.66(1.36-2.04)
Dementia symptoms (%)	21.0	38.1	**<0.001**	1.78(1.45-2.18)
Hospitalization the year before admission (%)	75.6	65.0	**0.011**	0.77(0.61-0.97)
Social admittance (%)	26.9	22.6	0.228	0.77(0.61-0.99)
Age mean	82.35	85.06	**<0.001**	1.03(1.02-1.05)
Gender: male (%)	27.9	36.5	**0.029**	1.36(1.11-1.68)