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RESEARCH PAPER

The impact of polypharmacy on 30-day COVID-related mortality in nursing home residents: a multicenter retrospective cohort study

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Key summary points

Aim The impact of polypharmacy on 30-day COVID-related mortality in nursing home residents was assessed after adjustment for age, sex, CCI, BMI and vaccination status.

Findings A significant positive association between a higher total number of medications and 30-day COVID-related mortality in NH residents was found. However, this association was attenuated when adjusted for dementia and use of PPI, vitamin D, antipsychotics and antithrombotics.

Abstract

Purpose Both the coronavirus (COVID-19) disease and polypharmacy pose a serious threat to nursing home (NH) residents. This study aimed to assess the impact of polypharmacy on 30-day COVID-related mortality in NH residents with COVID-19.

Methods Multicenter retrospective cohort study including NH residents from 15 NHs in the Netherlands. The impact of polypharmacy on 30-day COVID-related mortality was evaluated and assessed using multivariable logistic regression analyses with correction for age, sex, CCI, BMI and vaccination status.

Results In total, 348 NH residents were included, with a mean age of 84 years (SD = 8); 65% were female, 70% lived in a psychogeriatric ward, with a main diagnosis of dementia. 30-day COVID-related mortality was 27.3%. We found a significant, positive association between the total number of medications and 30-day COVID-related mortality (OR 1.09; 95% CI 1.001–1.20, $p = 0.046$), after adjustment for age, sex, Charlson Comorbidity Index (CCI), Body Mass Index (BMI) and vaccination status. After additional correction for dementia (model 2) and use of PPI, vitamin D, antipsychotics and antithrombotics (model 3), this effect remained positive, but was no longer significant.

Conclusion Nursing home residents with a higher number of medications and who were not vaccinated, had a higher 30-day COVID-related mortality. These findings have important implications for the management of COVID-19 in the frail NH population. As such they underline the importance of deprescribing on the one hand, but also of improving vaccination rates on the other.

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Keywords Polypharmacy · COVID-19 · Nursing home residents

Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), still disproportionately affects nursing home (NH) populations all over the world due to the high proportion of frail older adults with underlying chronic conditions, resulting in substantial morbidity and mortality [1, 2]. In this frail population, there is a high prevalence of polypharmacy, i.e., the concomitant use of 5 or more medications, which in itself is already associated with poor outcomes, such as unplanned hospitalizations, reduced functional capacity and increased all-cause mortality [3]. Since both COVID-19 and polypharmacy pose a threat to NH residents, it is important to gain insight into the impact of polypharmacy on clinical outcomes in NH residents with COVID-19.

Previous research has shown that increasing multimorbidity and polypharmacy are associated with a higher risk of developing COVID-19 [4]. Conversely, being diagnosed with COVID-19 also contributes to polypharmacy by increasing the average number of medications by an average of 2 (range 1–13), even 30 days post-COVID-19 [5]. According to some studies, polypharmacy seems to be associated with poor clinical outcomes, such as adverse drug reactions, acute kidney injury, developing severe COVID-19 (compared to non-severe COVID) and mortality, while other studies reported no significant differences between survivors and non-survivors [6–10]. One of the studies that showed that polypharmacy increased the risk of developing severe COVID-19 also showed that this increased risk was promoted by specific medications, such as proton pump inhibitors (PPIs) or antipsychotics, such as haloperidol, risperidon or clozapine [10].

On the other hand, several medications were found to possibly prevent severe COVID-19 or COVID-19-related mortality. Tang et al. found that anticoagulants could decrease mortality in patients with severe COVID-19 [11]. A retrospective case series of Brouns et al. on nursing home residents showed that oral antithrombotics were associated with a lower mortality in the univariable analysis. However, this difference was attenuated after additional adjustments for sex, age and comorbidity [12].

While these studies examined the impacts of polypharmacy on COVID-19 patients in general, little is known about the impact of polypharmacy on COVID-19 survival among residents of nursing homes. Understanding the impact of polypharmacy on COVID-19-related outcome might help to improve the care and treatment of this frail population.

The aim of this multicenter retrospective cohort study was to determine the impact of polypharmacy on 30-day COVID-related mortality in nursing home residents in the Netherlands.

Methods

Between March 2020 and December 2021, a multicenter retrospective cohort study of nursing home residents with COVID-19 was performed in 15 nursing homes of the nursing home organization Zuyderland in Sittard, the Netherlands. During these months, there were 4 coronavirus exacerbation waves. The Alfa variant was dominant from February 2020 until May 2020, from September until December 2020, and from March until June 2021, while the Delta variant was dominant from September 2021 until December 2021. In the Netherlands, the vaccination program started on 6 January 2021, and the first to be vaccinated were residents of nursing homes.

In the Netherlands, admission to a nursing home is only possible if permanent disabilities and comorbidities have led to severe care dependency for activities of daily living (ADL) and instrumental activities of daily living (iADL) and 24-h long-term institutional care is needed. The participating NHs have somatic wards for residents with physical diseases as well as psychogeriatric wards, which are primarily inhabited by residents with dementia. These NHs range from small scale homes with 30 beds to large-scale homes with 150 beds, adding up to a total capacity of 1459 beds.

NH residents were included if they lived in a long stay ward and had a laboratory-confirmed diagnosis of COVID-19, represented by a positive result on the reverse-transcriptase polymerase chain reaction (rRT-PCR) assay for SARS-CoV-2. There were no exclusion criteria.

All included residents received the same medical care for COVID-19, in accordance with national guidelines, including oxygen therapy, dexamethasone, antibiotics in case of a bacterial superinfection and/or low-molecular-weight heparin in patients without anticoagulants. Patients who were likely to die from COVID-19 received palliative care within the NHs.

Data collection

The following data were retrospectively obtained from the medical records: age, sex, nursing home ward (somatic or psychogeriatric), medical history, body mass index (BMI), medication use and date of death (if applicable). Based on the participants' medical histories, the comorbidity levels were assessed by calculating the Charlson Comorbidity Index (CCI). The primary outcome of this study was 30-day

COVID-related mortality. All data were treated confidentially and stored securely.

Data analysis

Primary outcome was COVID-related mortality 30 days after a positive rRT-PCR test. The characteristics of survivors and non-survivors were compared using independent-samples t-tests for numerical variables and the chi-square test or Fisher's exact test for categorical variables. Numerical variables were expressed as mean with standard deviation (SD), while categorical variables were expressed as number and percentage of residents. The effects of the total number of medications used at time of a positive COVID PCR test on mortality were calculated with multivariable logistic regression analyses. The effects are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs), correcting for three sets of potential confounders (models 1–3). Model 1 included age, sex, CCI, BMI, and the vaccination status (fully, partially, or not vaccinated) as potential confounders, while model 2 additionally included dementia; model 3 included the same variables as model 2, but also corrected for some of the medication groups that are prescribed most frequently for NH residents: PPI, vitamin D, antipsychotics, antithrombotics [13].

As the effects of the total number of medications used might depend on vaccination status and dementia, two-way interaction terms were included and tested in all three models. A top-down procedure was applied on these interaction terms, i.e., removing the least significant interaction term (highest p value) if it was not significant. In addition, the results of the final models 1, 2 and 3 were compared using likelihood ratio tests. The same models were analyzed using logistic mixed models and generalized estimating equations (GEE), accounting for the correlation between residents within the same NH. As the intra-class correlation (ICC) could not be estimated reliably (close to 0, but negative), it was set equal to 0, which reduces these analyses to logistic regression analyses. All analyses were performed using SPSS Statistics for Windows (version 26.0, Armonk, N.Y., USA, IBM Corp.). A two-sided p value of $p \leq 0.05$ was considered statistically significant. This study was approved by the medical ethical review board of Zuyderland. (METC-Z Z2021109).

Results

In total 348 nursing home residents who suffered from COVID-19 were included, 227 of whom (65%) were female. The mean age was 84 years (SD = 8). Of the participating residents, 242 (70%) lived in psychogeriatric wards with a main diagnosis of dementia, and the remaining 106 (30%) residents lived in a somatic ward with a main diagnosis of post-stroke status, chronic obstructive pulmonary disease (COPD), heart failure, Parkinson's disease, or other neurodegenerative diseases. The mean CCI was 7 (SD = 2), the mean BMI was 24.2 (SD = 5.1) and the mean total number of medications used was 6 (SD = 3). On the day of the positive rRT-PCR test result, 109 (31%) residents were fully vaccinated, 23 (7%) were partially vaccinated and 216 (62%) were not vaccinated. Of the unvaccinated residents, 4 residents had refused vaccination and 212 residents were infected with COVID-19 before vaccination was available. None of the participating residents were hospitalized during their COVID-19 infection. See also Table 1.

COVID-related mortality within 30 days after a positive rRT-PCR-test was 27.3% (95 out of 348). All non-survivors died from COVID-19, as confirmed by the nursing home physician. Most demographic characteristics were similar between survivors and non-survivors. Of the non-survivors, more were male ($p = 0.044$) and not fully vaccinated (not vaccinated or partially vaccinated, $p = 0.019$), more used a higher number of medications ($p = 0.013$) and more received a PPI or antiplatelet therapy (APT) ($p = 0.004$ and $p = 0.026$ resp.).

Of the three models that were considered in the multivariable logistic regression analyses, model 1 showed a significant positive association between a higher total number of medications and higher 30-day COVID-related mortality (OR 1.09; 95% CI 1.001–1.20, $p = 0.046$), after adjustment for age, sex, CCI, BMI and vaccination status. As shown in model 2, after adjusting for the diagnosis dementia, this association was similar, but not statistically significant anymore (OR 1.09; 95% CI 0.995–1.20, $p = 0.063$). Note that in model 2, the association between dementia and 30-day COVID-related mortality was not statistically significant (OR 0.94; 95% CI 0.53–1.67, $p = 0.846$).

Model 3 showed no statistically significant association between the use of PPI, vitamin D, antipsychotics or antithrombotics and 30-day COVID-related mortality. Based on likelihood ratio tests, model 1 was preferred, as the more complex models 2 and 3 did not fit the data significantly better than model 1 ($p = 0.846$ and $p = 0.594$, respectively).

Table 2 shows that in all three models, COVID-19 vaccination was associated with lower 30-day COVID-related mortality in nursing home residents (model 1, fully versus not vaccinated: OR 0.56; 95% CI 0.32–0.97, $p = 0.039$; partially versus not vaccinated: OR 0.20; 95% CI 0.04–0.88, $p = 0.034$).

Also, a higher age was associated with a higher 30-day COVID-related mortality ($p = 0.031$, 0.031, 0.027 respectively). This association did not attenuate after adjustment for sex, CCI, BMI, vaccination status, total number of medications, diagnosis of dementia and the different medication groups (OR 1.04; 95% CI 1.005–1.08, $p = 0.027$).

Table 1 Characteristics of nursing home residents with COVID-19

Baseline	Total ($N=348$)	Non-survivor ($N=95$)	Survivor ($N=253$)	p value
Women, *n* (%)	227 (65%)	54 (57%)	173 (68%)	**0.044**
Men, *n* (%)	121 (35%)	41 (43%)	80 (32%)	
Age, mean (SD), y	84 (8)	86 (8)	84 (7)	0.066
Ratio ward				0.423
Psychogeriatric, *n* (%)	242 (70%)	63 (66%)	179 (71%)	
Somatic, *n* (%)	106 (30%)	32 (34%)	74 (29%)	
Main diagnosis				0.724
Dementia, *n* (%)	246 (71%)	64 (67%)	182 (72%)	
CVA, *n* (%)	51 (15%)	16 (17%)	35 (14%)	
Parkinson's disease, *n* (%)	14 (4%)	6 (6%)	8 (3%)	
COPD, *n* (%)	12 (3%)	3 (3%)	9 (4%)	
Heart failure, *n* (%)	12 (3%)	3 (3%)	9 (4%)	
Other, *n* (%)	14 (4%)	4 (4%)	10 (4%)	
Vaccination				**0.019**
Full, *n* (%)	109 (31%)	24 (25%)	85 (34%)	
Partial, *n* (%)	23 (7%)	2 (2%)	21 (8%)	
None, *n* (%)	216 (62%)	69 (73%)	147 (58%)	
CCI, mean (SD)	7 (2)	7.4 (2.1)	6.6 (1.8)	**< 0.001**
BMI, mean (SD)	24.2 (5.1)	24.4 (5.3)	24.2 (5.0)	0.709
Medication use				
Total number of medicines, mean (SD)	6 (3)	6.9 (2.8)	6.1 (3.0)	**0.013**
Vitamin D, *n* (%)	122 (35%)	32 (34%)	90 (36%)	0.742
PPI, *n* (%)	154 (44%)	54 (57%)	100 (40%)	**0.004**
Antipsychotics, *n* (%)	86 (25%)	23 (24%)	63 (25%)	0.894
Antithrombotics, *n* (%)	210 (60%)	64 (67%)	146 (58%)	0.101
VKA, *n* (%)	23 (7%)	7 (7%)	16 (6%)	0.727
DOAC, *n* (%)	60 (17%)	12 (13%)	48 (19%)	0.163
APT, *n* (%)	125 (36%)	43 (45%)	82 (32%)	**0.026**
$LMWH_a$, *n* (%)	5 (1%)	3 (3%)	2 (1%)	0.128

Data collected on the day of the positive rRT-PCR test

Statistical significant values ($p < 0.005$) are presented in bold

APT antiplatelet therapy, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *COPD* chronic obstructive pulmonary disease, *CVA* cardiovascular accident, *DOAC* direct oral anticoagulant, *LMWH* low-molecular-weight heparin, *No* number of, *PPI* proton pump inhibitor, *rRT-PCR* real-time reverse-transcriptase polymerase chain reaction, *SD* standard deviation, *VKA* vitamin K antagonist, *y* year

[a]Fisher's exact test

Discussion

This multicenter retrospective cohort study is the first to show the impact of polypharmacy on 30-day COVID-related mortality in nursing home residents ($n=348$). We found a significant, positive association between the total number of medications and 30-day COVID-related mortality, which persisted after adjustment for age, sex, CCI, BMI and vaccination status. After adjustment for dementia and other potential confounders, this association was similar, but not statistically significant anymore, which could be related to the relatively small sample size. An interesting additional finding was the observation that non-survivors were more often unvaccinated, and this association was not attenuated after adjustment for age, sex and other potential confounders.

Our finding that polypharmacy is associated with poor outcome in the NH population is in line with the findings of studies on other populations, which showed that severe COVID-19 was associated with polypharmacy and also that patients in NH facilities are potentially more exposed to polypharmacy and thus to medication-related errors [5, 10]. A recent study by Blaszczyk et al. also showed that 1 in 5 NH residents with a COVID-19 diagnosis developed a

Table 2 Three models of multivariable logistic regression analyses to explore the association between clinical characteristics and 30-day COVID-related mortality in nursing home residents with COVID-19

Characteristics	Model 1 OR (95% CI)[a]	*p* value	Model 2 OR (95% CI)[a]	*p* value	Model 3 OR (95% CI)[a]	*p* value
Age (years)	1.04 (1.004–1.08)	**0.031**	1.04 (1.004–1.08)	**0.031**	1.04 (1.005–1.08)	**0.027**
Sex—female	0.67 (0.39–1.14)	0.138	0.67 (0.39–1.14)	0.138	0.65 (0.38–1.13)	0.125
Male	Reference		Reference		Reference	
CCI (unit)	1.14 (0.99–1.30)	0.065	1.14 (0.99–1.30)	0.065	1.13 (0.98–1.30)	0.095
BMI (unit)	1.00 (0.95–1.05)	0.967	1.00 (0.95–1.05)	0.977	1.003 (0.95–1.05)	0.905
Vaccination status		**0.019**		**0.020**		**0.021**
Fully vaccinated	0.56 (0.32–0.97)	**0.039**	0.56 (0.32–0.99)	**0.046**	0.56 (0.32–0.99)	**0.045**
Not vaccinated	Reference		Reference		Reference	
Partially vaccinated	0.20 (0.04–0.88)	**0.034**	0.20 (0.04–0.88)	**0.033**	0.20 (0.04–0.90)	**0.036**
No. of medications (unit)	1.09 (1.001–1.20)	**0.046**	1.09 (0.995–1.20)	0.063	1.08 (0.97–1.21)	0.157
Dementia						
Yes			0.94 (0.53–1.67)	0.846	0.97 (0.54–1.76)	0.927
No			Reference		Reference	
PPI use						
Yes					1.61 (0.89–2.91)	0.118
No					Reference	
Vitamin D use						
Yes					0.74 (0.43–1.29)	0.295
No					Reference	
Antipsychotics use						
Yes					1.09 (0.59–2.00)	0.792
No					Reference	
Antithrombotics use						
Yes					0.82 (0.44–1.51)	0.519
No					Reference	

Interactions were not significant, therefore not included in final models that are presented

Model 1: vaccination status with no. of medications $p = 0.275$

Model 2: vaccination status with no. of medications $p = 0.187$; no. of medications with dementia $p = 0.779$

Model 3: vaccination status with no. of medications $p = 0.243$; no. of medications with dementia $p = 0.816$

Statistical significant values ($p < 0.005$) are presented in bold

APT antiplatelet therapy, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *DOAC* direct oral anticoagulant, *No* number of, *PPI* proton pump inhibitor, *OR* odds ratio, *VKA* vitamin K antagonist

[a]Likelihood ratio tests—model 3 vs 2: $p = 0.454$; model 2 vs 1: $p = 0.846$; model 3 vs 1: $p = 0.594$

new, potentially dangerous drug-drug interaction [14]. This finding further emphasizes the importance of our study.

In addition to the number of medications, specific medication classes are of particular importance. These medications are among the most prescribed in NHs and are well-known indicators of overprescribing. Also, these medication classes have specific side effects that might increase the risk of adverse outcomes. For example, following the onset of the COVID-19 pandemic, previous studies have shown that NH residents were increasingly prescribed psychotropic, anticonvulsant, and opioid medications [15, 16]. This is probably due to the fact that otherwise favorable non-pharmacological interventions were deemed less appropriate due to isolation measures or had lower priority in times of limited resources, including lack of staff [16]. This potentially excessive prescribing behavior may pose an important threat to NH residents' health, as it might lead to increased confusion, sedation or falls [17].

Another medication class of particular interest are antithrombotics, as our univariable analysis showed that the use of PPI and APT was more common among non-survivors. Currently, there is conflicting evidence regarding the benefit of anticoagulant therapy in general and of APT in particular, as studies in different populations yielded mixed results [18, 19].

The finding that a higher percentage of non-survivors were unvaccinated may also explain why the COVID-related mortality found in this study (27.3%) was lower

than expected. Given the greater frailty and older age of the multimorbid NH residents in our study, we expected a higher mortality [13]. Our findings support the hypothesis that vaccination reduced the risk of COVID-19-related mortality in NHs.

The present study offers relevant insights into the impact of polypharmacy and COVID-19 on NH residents and shows the importance of vaccination in NH residents. Nevertheless, a note of caution is due since there are several study limitations, such as the retrospective design and the observational nature of the study. Also, data for this study were collected between March 2020 and December 2021, hence they most likely did not include the novel omicron variant of SARS-CoV-2. This new variant appears to be associated with a reduced risk of hospital admission and mortality. It is unclear whether these study results also apply on this new omicron variant.

Despite these limitations, our study provides relevant information and insight into the impact of polypharmacy on 30-day COVID-related mortality in NH residents. Additional studies are needed to evaluate the impact of different kinds of medication groups on mortality within the NH population, as an approach to reduce mortality due to COVID-19 among NH residents.

Conclusion and implications

Nursing home residents with a higher number of medications and who were not vaccinated, had a higher 30-day COVID-related mortality. These findings have important implications for the management of COVID-19 in the frail NH population. As such they underline the importance of deprescribing on the one hand, but also of improving vaccination rates on the other.

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Author contributions Study concept and design: AGRV, JMGAS, BS, RJ and BW. Acquisition of data: AV. Analysis and interpretation of data: AGRV, BW, JMGAS, BS and RJ. Drafting of the manuscript: AGRV, BS, BW, JMGAS and RJ. Critical revision of the manuscript for important intellectual content: JMGAS, BS, BW, RJ, and AGRV.

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Data availability The authors declare that the data supporting the findings of this study are available within the article and its supplementary files.

Declarations

Conflict of interest The authors have no conflict of interest to report, financial or otherwise.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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