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International Journal of Infectious Diseases 109 (2021) 192–194

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Drug exposure may have a substantial influence on COVID-19 prognosis among residents of long-term care facilities: an exploratory analysis

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ARTICLE INFO

Article history:
Received 9 June 2021
Revised 1 July 2021
Accepted 3 July 2021

Keywords:
Covid-19
SARS-CoV-2
long-term care facilities
drug exposure
inhaled corticoids
statins
ACE2 inhibitors

ABSTRACT

Objectives: To explore the association between drug exposure and SARS-CoV-2 prognosis among elderly people living in long-term care facilities (LTC)

Design: We carried out a cross-sectional study among old people living in LTC that had a proven SARS-CoV-2 infection, including socio-demographic data, comorbidities and drug intake at the moment of the diagnosis. The study was focused on ACE2 inhibitors, ARA-II blockers, inhaled bronchodilators, oral corticoids, platelet antiaggregants, oral anti-coagulants, statins and Vitamin D.

Results: 1 306 individuals were included, with a mean age of 86.7 years, and 72.3% were females. The case fatality rate was 24.4%. Among the studied exposures platelet antiaggregants were the most prevalent (24.7%). After adjusting for propensity score, the intake of inhaled corticoids (OR 0.73; p=0.03) and statins (OR 0.65; p=0.03) were found to be protective factors of death, whereas ACE2 inhibitor showed an almost significant association (OR 0.73, p=0.07).

Conclusions: Considering the high prevalence of drug intake among elderly people, drug exposure may be an important Covid-19 disease modifier in LTC residents and should be considered when exploring prognostic risk factors associated to Covid-19.

Introduction and methods

Older people living in long-term care (LTC) facilities have been the population hardest hit by the Covid-19 pandemic. Recent estimates suggest that as much as 47% of first-wave Covid-19 fatalities in Western countries occurred in LTC facilities. (Comas-Herrera et al., 2020) This appalling statistic is related to the combination of optimal epidemiological conditions for the spread of SARS-CoV-2 in enclosed spaces crowded with a highly vulnerable population. One feature of this population that has received scant attention in this connection is drug consumption. LTC residents tend to be poly-medicated, with some of them taking up to a dozen or more different drugs. (Sluggett et al., 2020) Such drugs commonly include a wide array of pharmaceutical principles, but also anti-hypertensives, bronchodilators, anti-inflammatories, psychiatric medication, anti-osteoporotic treatments, statins and oral anticoagulants, and platelet antiaggregants. To explore the relation between the prevalent types of medication in LTC facilities and Covid-19 prognosis, we carried out a cross-sectional study among

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https://doi.org/10.1016/j.ijid.2021.07.007

LTC residents with SARS-CoV-2 infection as confirmed by RT-PCR test during the first wave of the pandemic (March–June 2020). The study population has been described elsewhere. (Suñer et al., 2021) We collected data on medication being consumed at the moment of the diagnosis from the clinical records of the LTC facility. Our focus was on those drugs that aroused most interest among clinicians, those for which evidence had been gathered previously and those with a plausible association with Covid-19 prognosis such as ACE2 inhibitors, ARA-II blockers, inhaled bronchodilators, oral corticoids, platelet antiaggregants, oral anti-coagulants, statins and Vitamin D. Participants were tested against recovery or death after adjusting for Propensity Score (PS) at day 15, day 30 and overall. PS included participant baseline clinical, autonomy and frailty scores and socio-demographic data.

Results

Data on drug intake and follow-up were recorded for 1 306 individuals, which represents 58.8% of the SARS-CoV-2-infected population living in LTC facilities from our study area (N = 2 221) during the study period. The mean age was 86.7 years (SD = 7.3, range 65-105) and 72.3% were females. The overall Case Fatality Rate of our sample was 24.4% (n = 239), being higher among males than females (32.8% vs. 21.2%, $p < .001$). The median number of drugs, being taken per participant was 8 (including those not under study), with a range from 0 to 25 (Interquartile range of 5-10). At the time of SARS-CoV-2 diagnosis 381 individuals (29.2%) were consuming platelet antiaggregant, 323 (24.7%) ACE2 inhibitor, 244 (18.7%) vitamin D derivatives, 224 (17.2%) statins, 172 (13.2%) ARA-II blockers, 195 (14.9%) anticoagulants, 112 (8.4%) inhaled corticoids and 88 (6.7%) oral corticoids (see Table 1 for detailed description). After PS adjustment we observed a protective association for inhaled corticoids (OR 0.52; 95%CI 0.3-0.9; $p = 0.03$), and statins (OR 0.65; 95%CI 0.4-0.9; $p = 0.03$), including a close to significant protective association with ACE2-antagonist intake (OR 0.73; 95%CI 0.5-1.0, $p = 0.07$) at 30-day mortality after Covid-19 diagnosis (see Table 2). We did not find evidence of interaction of inhaled corticoids with other bronchodilators (long-acting β agonists and long-acting muscarinic antagonists), or between the drugs studied among individuals with concomitant treatment.

Table 1
General prevalence of recorded drug exposures among the study sample

Drug	Total N	%	Death N	%	p
ACE 2 antagonists					
Captopril	9	0.7	1	1.1	0.7
Enalapril	270	20.7	54	20.0	.07
Cilazapril	1	0.1	0	0.0	0.7
Imidapril	1	0.1	0	0.0	0.7
Lisinopril	26	2.0	3	11.5	0.2
Ramipril	24	1.8	5	20.8	0.6
Fisinopril	1	0.1	0	0.0	0.7
ARB-II blockers					
Losartan	111	8.5	27	24.3	0.9
Candesartan	7	0.5	2	28.6	0.7
Olmasertan	3	0.2	2	66.7	0.2
Valsartan	38	2.9	14	36.8	.07
Telmisartan	3	0.2	0	0.0	0.9
Irbesartan	4	0.3	1	25.0	0.9
Statins					
Atorvastatina	80	6.1	20	25.0	0.9
Lovastatina	3	0.2	0	0.0	0.5
Rosuvastatina	5	0.4	1	20.0	0.7
Sinvastatina	136	10.4	29	21.3	0.4
Anticoagulant					
Acenocumarol	83	6.4	18	21.7	0.5
Warfarina	4	0.3	2	50.0	0.2
Dabigatran	11	0.8	2	18.2	0.6
Edoxaban	8	0.6	1	12.5	0.4
Apixaban	53	4.1	10	18.9	0.3
Rivaroxaban	22	1.7	3	13.6	0.2
Dalteparina	1	0.1	0	0.0	0.8
Enoxaparina	10	0.8	1	10.0	0.3
Heparina	3	0.2	2	66.7	0.1
Platelet antiaggregant					
AAS	328	25.1	93	28.4	.06
Ticagrelor	1	0.1	0	0.0	0.8
Clopidrogrel	60	4.6	16	26.7	0.7
Triflusal	5	0.4	3	60.0	.07
Inhaled corticosteroids					
Budesonida	55	4.2	10	18.2	0.3
Beclometasona	46	3.5	11	23.9	0.9
Fluticasona	13	1.0	1	7.7	0.2
Fludrocortisona	1	0.1	0	0.0	0.8
Oral corticosteroids					
Deflazacort	2	0.2	1	50.0	0.4
Prednisona	10	0.8	2	20.0	0.6
Prednisolona	41	3.1	14	34.1	0.1
Metilprednisolona	30	2.3	13	43.3	0.02
Dexametasona	9	0.7	0	0.0	0.1
Vitamine D derivatives (overall)	252	19.3	45	18.8	0.04

Discussion and conclusions

Notwithstanding that with our study design we cannot conclude a causal effect between drugs intake and clinical prognosis, our results are consistent with most of the previously published evidence that ACE-2 antagonists, statins and inhaled corticoids may have a protective effect against severe Covid-19, (Nicolau and Bafadhel, 2020, Kurdi et al., 2020, Lee et al., 2020) but not antithrombotic therapy, oral corticoids, ARA-II blockers and Vitamin D in the dosages typically given to the elderly. The most noteworthy finding, due to their potential as preventive therapy against severe Covid-19, is the protective association of inhaled corticoids. A recently published clinical trial strongly suggests this positive effect with regard to complicated Covid-19 in the general population. (Ramakrishnan et al., 2021). Considering the prevalence of drug intake and the high attack rates of the disease in the LTC population during the first wave of the pandemic, the fraction of prevented deaths attributable to consumption of these drugs may have been substantial. It is worth noting that the interaction between inhaled corticoids, ACE-2 antagonists and statins and Covid-19 is most probably mediated by their effect as inflammatory modulators, at the local level in alveolar epithelia (ACE-2 inhibitors and inhaled corticoids) or at systemic level (statins). Given that ageing is related to a more pro-inflammatory status (Casucci et al., 2020) our observations may not be straightly translated to the general population. Furthermore, the protective effect of these drugs could be due to long-term intake having caused chronic changes in the tissues targeted (i.e. lower or higher expression of ACE-2 receptor in respiratory epithelia). However, further exploration of these effects among residential populations may provide a better understanding of the physiopathology of Covid-19 as well as some clues for future therapeutic or preventive drug targets. The most important conclusion from our findings together with the previously collected evidence is that drug exposure may be an important Covid-19 disease modifier in LTC residents and should be considered when exploring prognostic risk factors.

Acknowledgements

Our heartfelt gratitude to all nursing homes teams for facilitating the collection of information required for this study, and to Yolanda García Murillo for their support during the data collection process.

Table 2
Association analysis between bad outcome and drug exposure (adjusted by PS)*,**

Drug family	Mortality at day 15 OR	95% CI	p	Mortality at day 30 OR	95%CI	p	Overall mortality OR	95%CI	p
ACE2 inhibitor	0.78	(0.5-1.2)	0.2	0.73	(0.5-1.0)	0.07	0.74	(0.5-1.0)	0.08
Inhaled corticoids	0.61	(0.3-1.1)	0.1	0.52	(0.3-0.9)	0.03	0.58	(0.3-1.00)	0.05
Statins	0.77	(0.5-1.2)	0.2	0.65	(0.4-0.9)	0.03	0.69	(0.5-1.0)	0.06
Vitamin D derivatives	0.87	(0.6-1.3)	0.5	0.8	(0.6-1.2)	0.2	0.79	(0.6-1.1)	0.2
Platelet antiaggregants	1.14	(0.8-1.6)	0.4	1.09	(0.8-1.5)	0.6	1.09	(0.8-1.5)	0.6
Anticoagulants	0.91	(0.6-1.4)	0.7	0.78	(0.5-1.2)	0.5	0.76	(0.5-1.1)	0.2
Oral corticoids	1.27	(0.7-2.2)	0.4	1.57	(0.9-2.6)	0.08	1.68	(1.0-2.8)	0.04
ARA-II blockers	1.23	(0.7-1.7)	0.6	1.09	(0.7-1.6)	0.7	1.01	(0.7-1.5)	0.9

* PS included age, gender, respiratory, cardiovascular or cerebrovascular comorbidities, hypertension, dementia, diabetes mellitus type II, Barthel score, frailty score, size of the LTC facility in number of residents.
** Adjustments included drugs under study

Conflicts of interest

None to declare

Ethical approval

The study was approved by the Ethics Board of the Region's reference hospital and registered under reference number PI-20-349.

Funding

No specific sources of funding were used for this study

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