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Original Article

Risk factors for developing symptomatic COVID-19 in older residents of nursing homes: A hypothesis-generating observational study

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Abstract

Objectives: To identify which risk factors were associated with developing Coronavirus Disease-19 (COVID-19) infection, with symptoms, in institutionalized older people. **Methods**: A 1-year longitudinal multi-center study was conducted in 5 nursing homes (NHs) over the period December 2019 to March 2021. Inclusion criteria included being a permanent resident in the NH, aged 65 years or older, and a positive diagnosis of COVID-19 objectively confirmed by a diagnostic test. A descriptive and bivariate analysis was performed, calculating relative risk (RR) with 95% confidence intervals and statistical significance at $p<0.05$. **Results**: Of the total sample of 78 individuals who tested positive for COVID-19, the mean age was 84.6 years (SD=±7.8), 62 (79.5%) were female; 40 (51.3%) participants presented with COVID-19 symptoms. Living in a private NH (RR=3.6, 95% CI [1.2–11.0], p=0.023) and having suffered a stroke (RR=4.1, 95% CI [1.1–14.7], p=0.033) were positively associated with developing COVID-19 infection with symptoms. **Conclusions**: Having suffered a stroke and living permanently in a private NH were positively associated with symptomatic COVID-19 in this sample of institutionalized older people.
Clinical Trials ID: NCT04297904

Keywords: COVID-19, Geriatric Medicine, Infectious Disease, Nursing Care

Introduction

In December 2019, the Coronavirus Disease-19 (COVID-19) pandemic, or severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), started to have a major impact on society[1]. The pandemic as had unprecedented consequences on worldwide health and economic systems[2]. The severity and mortality risk of COVID-19 is associated with age, so that older people living in nursing homes (NHs) have been particularly at risk of poor outcomes during this pandemic[1].

The main symptoms of COVID-19 in older people are fever, respiratory difficulties, cough, diarrhoea, sudden urinary incontinence (UI) and disorientation or delirium[3]. Fever, defined as a temperature above 37.5°, is one of the

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most common symptoms in COVID-19 viral infection[4], along with respiratory distress and cough, defined as increased respiratory rate and the need to keep the airway clear[4]. Gastrointestinal symptoms were defined, in the context of COVID-19 infection, as intestinal distress: the main symptom was diarrhoea followed by nausea, vomiting and anorexia[4]. Different studies show clinical suspicion that COVID-19 infection leads to viral cystitis, causing an increase in urinary frequency with the onset of sudden UI[5]; sudden UI is a less frequent symptom in COVID-19 positive patients and it can be difficult to make a differential diagnosis in institutionalized older people[5]. Finally, delirium and disorientation due to COVID-19 are understood as fluctuating alterations of consciousness, inattention and reduced awareness. Some patients may show hallucinations[6]. However, there are many people that test positive for COVID-19 but who are asymptomatic. The estimated proportion of asymptomatic infections ranges from 18% to 81%[7].

The literature shows multiple risk factors associated with COVID-19 symptom severity and mortality, such as aging, male sex, hospital admission required for COVID-19, having been hospitalized in the month before the admission for COVID-19, malnutrition, cancer and a wide range of chronic health conditions[8].

Older people who reside in NHs, therefore, had a higher risk of complications and mortality from COVID-19 infection due to their more advanced age, greater number of underlying chronic conditions, cognitive and physical impairments and greater frailty than the general community dwelling older population[3,8]. NHs are particularly at risk when dealing with an infectious disease outbreak, such as influenza virus, norovirus or the current COVID-19[9]. Environmental factors must also be considered: space, inadequate infrastructure and difficulty in maintaining social distance between residents and NH staff all increased the risk of infection. It is estimated that 69% of deaths due to COVID-19 in Spain between April and June 2020 were in older people living in NHs[4]. In Catalonia, over this period, 3965 people died from a variety of causes in NHs. Of these, 1133 died from COVID-19 in private NHs and 222 in public NHs[4].

Even before the COVID-19 pandemic, Fité et al., (2019)[10], reported that the staffing level and health of Catalan NHs personnel was precarious. With the COVID-19 outbreak, the staffing situation worsened further, being exposed to high levels of workload and social pressure[11]. Some studies[9,11] indicate that factors such as lack of staff due to COVID-19 infection, their scarce training in the management of infectious diseases or in the correct use of personal protective equipment (PPE), insufficient foresight and contingency planning due to lack of coordination of health, social services and NHs, all provided the perfect environment for COVID-19 to spread rapidly among residents and staff of NHs.

To our knowledge, this is the first study to collect sociodemographic and health-related data within multiple NHs just prior to the onset of the COVID-19 pandemic. This has allowed identification of which risk factors were associated with developing COVID-19 infection with symptoms in institutionalized older people. This information may be useful to better understand the causality of COVID-19 occurrences and thus be able to design strategies aimed at its prevention in the future.

Methods

Study design

An observational hypothesis-generating design within a one-year cohort longitudinal multi-centre study (Clinical Trials ID: NCT04297904) that followed the standards of STROBE (Strengthening the Reporting of Observational studies in Epidemiology) for cohort studies[12]. It is a sub-study of the OsoNaH project[13] and baseline data collection was conducted between December 2019 and March 2020 (before the state of alarm in Spain due the COVID-19 pandemic). The study was carried out in five NHs in Osona (a region of Central Catalonia, Spain).

Participants

All residents aged 65 years or older who were living in the NH on a permanent basis and who had a positive diagnosis of COVID-19 objectively confirmed by a diagnostic reverse transcription polymerase chain reaction (RT-qPCR) or serologic test were included. Exclusion criteria were residents who had COVID-19 diagnostic tests performed and the results were negative, residents who had no COVID-19 diagnostic test performed, residents in a coma or in palliative care (short-term prognosis of death), or who refused (or their legal guardian refused) to participate in the study.

Study procedures

Before starting data collection, each NH director consented to join the study. They then, with the study team, selected all residents that met the inclusion criteria (permanent resident, aged 65 or older, not in a coma or in receipt of palliative care). Depending on capability, the residents or their legal guardians were approached about the project and those who agreed to participate signed informed consent. Prior to the start of the project the research team collecting the data was trained in the use of all tools and tests. The reliability of the data collected through the health and sociodemographic questionnaires was evaluated by calculating the Kappa index and the interclass correlation coefficient (ICC) for the data of the first 20 residents enrolled. The ICC scores were greater than 0.75 on all physical tests. The results of these 20 residents were included in the final total study sample.

Outcome measurements

The main outcome, symptomatic COVID-19 infection, was reported if the resident tested positive for RT-qPCR and/or serologic testing during the 1-year follow-up period and

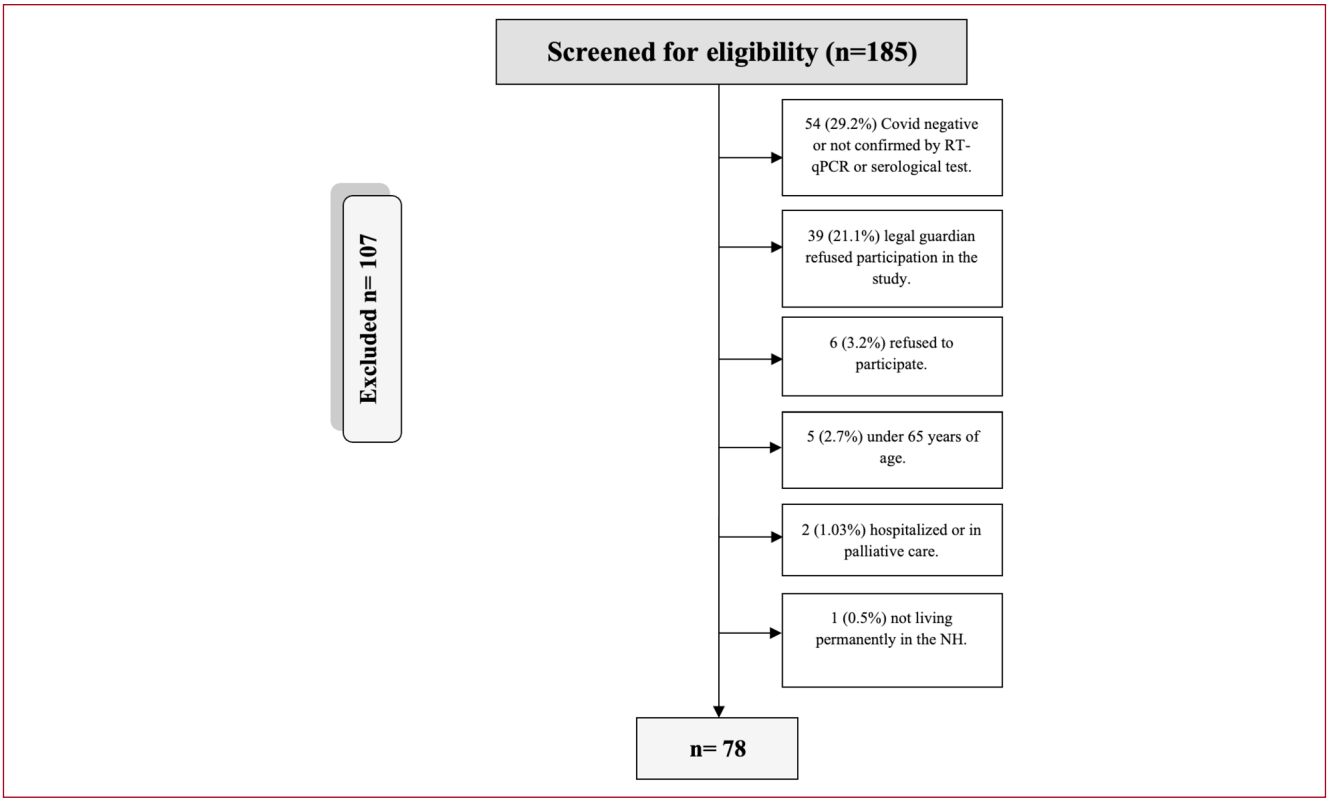

Figure 1. Flow chart of the sampling process.

experienced the presence of at least one COVID-19-related symptom (fever, respiratory distress, cough, diarrhoea, sudden UI, and disorientation or delirium)[4]. In order to differentiate the symptoms from the typical comorbidities of older people, those with a positive COVID-19 diagnosis were first identified by diagnostic tests.

Subsequently, with the collaboration of the NH professionals, a list was made of symptoms that appeared at the same time as the diagnosis of COVID-19, which were not present in the person before. We followed the methodology used in the article published in 2020 by Lopez de la Iglesia[14] and verified, according to the evidence, that the symptoms that appeared had also been identified as COVID-19 symptoms by other studies. Evidence showed that more than 50% of COVID-19 positive residents could be asymptomatic. Therefore, we performed a RT-qPCR testing on all residents, whether or not they were symptomatic, following the same methodology as Lopez de la Iglesia[14]. The presence of at least one COVID-19-related symptom with a positive COVID-19 test, the primary variable, was collected in two waves: at six months and one year after baseline.

At baseline, in December 2019 just prior to the onset of the COVID-19 pandemic, sociodemographic information and medical history, such as age, sex, education level, marital status, children, chronic diseases, smoking and drinking habits, type of NH and hospitalizations, was obtained from NH records and checked with NH professionals. Anthropometric variables such as body mass index (BMI), weight and height were measured with a Seca 213 measuring device, the Tanita TBF-300. Nutritional status was assessed using the Mini Nutritional Assessment (MNA)[15]. Continence status was reported using section H of the Minimum Data Set (MDS) version 3.024[16]. Functional capacity was measured using the modified Barthel Index, excluding continence items[17]. Cognitive status was assessed using the Pfeiffer Scale[18]. The SARC-F questionnaire was used to determine the risk of developing sarcopenia[19].

Sedentary behaviour (SB) was recorded using the activPAL3TM activity monitor (PAL Technologies Ltd., Glasgow, UK), considered the gold standard on assessing SB and postural changes in older adults[20]. The device was placed in the middle of the right thigh, or on the non-plegic thigh in residents who had had a stroke and worn for 7 consecutive days[21]. The following variables were extracted: average (per day) waking hours, steps, time in upright position, time sitting, time of SB bouts, number of sit to stand transitions, and percentage time sitting in waking hours.

Frailty was assessed using the Clinical Frailty Scale

(CFS)[22]. Physical capacity was examined using the Short Physical Performance Battery (SPPB)[23]. The authors received permission to use all of these instruments from the copyright holders.

The approximate time to complete the physical tests and questionnaires with each resident was 30-45 minutes. For further details, please refer to the Clinical Trials protocol (Clinical Trails ID: NCT04297904) of the Osonah Project[13].

Statistical analysis

A descriptive analysis was performed indicating absolute and relative frequencies for categorical variables. Bivariate analysis was applied using the Chi-square test (or Fisher's test, when necessary) and the linear Chi-square test for dichotomous and ordinal variables, respectively. Odds ratio was transformed into Relative Ratio (RR), which was used as measure of association. Multivariate analysis was performed by linear logistic regression with robust variance. A level of $p<0.05$ was considered statistically significant. Data was analyzed with SPSS version 27 (SPSS Inc., Chicago IL).

Results

The initial study sample in the 5 NHs was 185 participants. Thirty-nine individuals (21.1%) were excluded at baseline because the legal guardian refused participation in the study, 6 residents with capacity (3.2%) did not want to participate, 5 (2.7%) were younger than 65 years, 2 (1.0%) were hospitalized at baseline or in palliative care (short-term prognosis of death) and 1 (0.5%) did not live permanently in the NH. After 12 months of follow-up, 54 (29.2%) did not test positive for COVID-19 or had not been tested for COVID-19 and were therefore excluded from the analysis on associations.

A total of 78 residents were included, representing 41.2% of the total number of residents initially recruited in the five NHs (Figure 1).

The mean age of the residents was 84.6 years (SD=7.8) of which 46 (59%) were over 86 years old. Sixty-two (79.5%) were females and 59 (75.7%) were single or widowed. Sixty-one residents (78.2%) had one or more children, 4 (5.1%) were smokers and 9 (11.6%) were alcohol consumers. Thirty-eight (48.7%) had been living permanently in the NH for more than two years. Fifty-one (65.4%) lived in a subsidized NH and 27 (34.6%) in a private NH.

Chronic Pathologies

Forty-three (55.1%) participants had pluripathology (more than 5 diagnosed chronic pathologies). The most relevant chronic conditions were: hypertension (64.1%), dementia (52.6%), cardiac pathology (43.6%) and previous stroke (19.2%).

Intellectual, Continence, Nutritional and Physical Conditions

Fifty-five (70.5%) residents had moderate or severe cognitive impairment. Twenty-eight (35.9%) had UI and 14 (17.9%) faecal incontinence. Eleven (14.1%) residents had lost weight in the last year, 25 (32.1%) were malnourished or at risk of malnutrition and 46 (59.0%) were obese. Regarding functional capacity, 62 (79.5%) had moderate or severe dependence and of these residents, 17 were post-stroke patients in which the 41,2% had severe or total dependency. Thirty-five (44.9%) had risk of sarcopenia, 14 (51.3%) had moderate, severe or extreme frailty and 40 (51.3%) reported physical disability.

Sedentary Behaviour Pattern

Residents were awake for an average of 11.1 (SD: 1.1) hours. Of this, they spent an average of 82.6% (SD: 16.4) of their waking hours in SB, with a mean of 9.1 (SD: 1.6) hours in SB. The average SB bout was 62.3 (SD: 64.5) minutes. In their waking day they performed 19.0 (SD: 14.0) sit to stand transitions, had an average of 1.9 (SD: 1.9) hours in an upright position and walked 1599.0 (SD: 2551.0) steps.

Follow-up

At twelve months, 40 (21.6%) deaths were registered, of which 19 (10.3%) were COVID-19 deaths. One (0.5%) person in the study was not followed up as she moved out of the NH. Forty individuals (51.3%) from the total sample of residents who tested positive had COVID-19 symptoms. Other sociodemographic and health conditions of residents with a confirmed diagnosis of COVID-19 are shown in Table 1.

Associations

In the bivariate analysis, symptomatic cases of COVID-19 were significantly associated with living in a private NH (p=0.008) and having had a stroke (p=0.019). The rest of the sociodemographic and health variables showed no significance (Table 2). In the multivariate analysis, living in a private NH and having had a stroke were positively associated with having symptomatic COVID-19, independent of age and sex. The final model was adjusted according to the Hosmer Lemeshow test (p=0.933).

Discussion

The emergence of COVID-19 represents a dynamic, specific and real threat to the health and wellbeing of older people. The main objective of this study was to identify whether the health and sociodemographic conditions of NH residents were associated with having COVID-19 infection with symptoms.

Only half of the COVID-19 positive NH residents had COVID-19 symptoms. The non-specific presentation of COVID-19 illness, where 'normal' COVID-19 symptoms are

Variables	Frequency (%)/ Mean (SD)
Education level	
Illiterate	19 (24.4)
Primary education	34 (43.6)
Secondary education/ University studies	25 (32.0)
Marital Status	
Married/ Partner	12 (15.4)
Single	12 (15.4)
Widowed	47 (60.2)
NR	7 (9.0)
Children	
0	17 (21.8)
1	20 (25.6)
+2	41 (52.6)
Chronic diseases	
Hypertension	50 (64.1)
Dementia	41 (52.6)
Cardiac pathology	34 (43.6)
Dyslipidemia	22 (28.2)
Kidney failure	21 (26.9)
Diabetes mellitus	19 (24.4)
Depression	18 (23.1)
Stroke	17 (21.8)
Digestive pathology	16 (20.5)
Cancer	15 (19.2)
Mental pathology	15 (19.2)
Osteoporosis	15 (19.2)
Pulmonary pathology	14 (17.9)
Hypothyroidism	12 (15.4)
Circulatory pathology	12 (15.4)
Parkinsons	10 (12.8)
Anaemia	9 (11.5)
Hospitalizations	16 (20.5)
Functional capacity (Barthel Index)	
Independence	4 (5.1)
Slight dependence	12 (15.4)
Moderate dependence	29 (37.2)
Severe dependence	33 (42.3)
Cognitive status (Pfeiffer Scale)	
No cognitive impairment	8 (10.3)
Mild cognitive impairment	13 (16.7)
Moderate cognitive impairment	20 (25.6)
Sever cognitive impairment	35 (44.9)
NR	2 (2.5)
Physical capacity (SPPB)	
Robust person	5 (6.4)
Pre frail person	10 (12.8)
Frail person	19 (24.4)
Disabled person	40 (51.3)
NR	4 (5.1)
Frailty (CFS)	
Excellent/ Acceptable/ Good	17 (21.8)
Vulnerable	6 (7.7)
Minimal frailty	13 (16.7)
Moderate frailty	17 (21.8)
Severe/ Extreme frailty	23 (29.5)
Terminal patient	-
NR	2 (2.5)

SD: Standard Deviation; SPPB: Short Physical Performance Battery; CFS: Clinical Frailty Scale; NR: Not reported due to COVID19 pandemic outbreak.

Table 1. Descriptive analysis of the sample of institutionalized older adults with confirmed diagnosis of COVID-19 (n=78).

not present, has previously been highlighted[24]. International comparisons of data considering symptoms and infections are difficult due to differences in testing capabilities and policies (particularly in the earlier part of the pandemic), different approaches to recording deaths, and differing definitions of what constitutes a NH[25].

In this sample, it was observed that having suffered a stroke and living in a private NH were positively associated with having symptomatic COVID-19, independent of age and sex. Previous studies have shown that older people with chronic conditions, including cerebrovascular pathology, had a higher risk of contracting COVID-19 infection with symptoms and consequently a higher risk of mortality from COVID-19[26,27]. However, the causative relationship between cerebrovascular events and COVID-19 is not conclusive[27]. Neurological pathologies have a component that compromises autoimmune aggression and, therefore, leads to the need for immunosuppressive or immunomodulatory

Table 2. Bivariate and multivariate analyses showing the association of the variables and symptomatic COVID-19.

Variable	Symptomatic COVID-19				Bivariate analysis		Multivariate analysis	
	Yes (n=40)		No (n=38)					
	n	*(%)*	*n*	*(%)*	*p/Fisher*	RR (95% CI)	*p*	*Adjusted* RR *(95% CI)*
Age								
-/= 85 years	14	45.2	17	54.8	0.380	1	0.991	1.00 (0.92-1.10)
+ 86 years	26	55.3	21	44.7		1.22 (0.78– 1.92)		
Sex								
Men	10	62.5	6	37.5	0.314	1	0.389	0.57 (0.16-2.01)
Women	30	48.4	32	51.6		0.73 (0.37 – 1.43)		
Marital status								
Married/Partner	5	41.7	7	58.3	0.636	1		
Single/Widowed	29	49.2	30	50.8		1.14 (0.67 – 1.97)		
Children								
0 – 1	16	43.2	21	56.8	0.177	1		
2+	24	58.5	17	41.5		1.37 (0.86 – 2.16)		
NH type								
State subsidized places	21	40.4	31	59.6	**0 .008***	1	**0.023***	3.64 (1.20-11.04)
Private	19	73.1	7	26.9			1.54 (1.11 – 2.15)	
Chronic diseases								
- 5 diseases	15	42.9	20	57.1	0.177	1		
5/ + diseases	25	58.1	18	41.9		1.36 (0.86 – 2.15)		
Stroke								
No	27	44.3	34	55.7	**0.019***	1	**0.033***	4.10 (1.12-14.72)
Yes	13	76.5	4	23.5		2.36 (0.97 – 5.74)		
Smoke								
No	27	51.9	25	48.1	1.000[a]	1		
Yes	2	50.0	2	50.0		0.96 (0.34 – 2.66)		
Alcohol								
No drinker	26	45.6	31	54.4	1.000[a]	1		
Drinker	4	44.4	5	55.6		0.98 (0.52 – 1.84)		
Hospitalizations								
No	33	53.2	29	46.8	0.499	1		
Yes	7	43.8	9	56.3		0.83 (0.50 – 1.38)		
Nutritional Status (MNA)								
Normal	8	42.1	11	57.9	0.490	1		
Malnutrition or risk	8	32.0	17	68.0		0.85 (0.53 – 1.36)		
Weight loss (MNA)								
No	35	53.8	30	46.2	0.606	1		
Yes	5	45.5	7	54.5		0.86 (0.47 –1.56)		
Obesity (BMI)								
No (- 30 BMI)	6	42.9	8	57.1	0.744	1		
Yes (=/+ 30 BMI)	22	47.8	24	52.2		1.09 (0.64 – 1.86)		

Table 2. *(Cont. from previous page).*

Variable	Symptomatic COVID-19				Bivariate analysis		Multivariate analysis	
	Yes (n=40)		No (n=38)					
	n	*(%)*	*n*	*(%)*	*p/Fisher*	RR (95% CI)	*p*	*Adjusted* RR *(95% CI)*
Urinary incontinence (MDS)								
No	18	64.3	10	35.7	0.086	1		
Yes	22	44.0	28	56.0		0.64 (0.36 – 1.11)		
Fecal incontinence (MDS)								
No	33	54.1	28	45.9	0.448	1		
Yes	6	42.9	8	57.1		0.80 (0.47 – 1.36)		
Functional capacity (Barthel Index)								
Independence/ slight/ moderate dependence	26	57.8	19	42.2	0.180	1		
Severe dependence	14	42.4	19	57.6		0.73 (0.46 – 1.15)		
Cognitive status (Pfeiffer Scale)								
Mild/ moderate impairment	22	53.7	19	46.3	0.846	1		
Severe impairment	18	51.4	17	48.6		0.95 (0.59 – 1.53)		
Physical capacity (SPPB)								
Robust/ pre frail/ frail	20	58.8	14	41.2	0.236	1		
Disabled	18	45.0	22	55.0		0.75 (0.46 –1.22)		
Frailty (CFS)								
Mild/Moderate	27	50.9	26	49.1	0.931	1		
Severe	13	52.0	10	48.0		1.02 (0.62 – 1.67)		
Risk of sarcopenia (SARC-F)								
No	12	57.1	9	42.9	0.530	1		
Yes	28	49.1	29	50.9		0.84 (0.48 – 1.47)		
% time in SB								
-/=85%	16	64.0	9	36.0	0.200	1		
+85%	13	46.4	15	53.6		0.67 (0.36 - 1.25)		

*[a]Fisher's exact text; * Statistically significant (<0.05); NH: Nursing Home; SB: Sedentary Behavior; MNA: Mini Nutritional Assessment; BMI: Body Mass Index; MDS: Minimum Data Set; SPPB: Short Physical Performance Battery; CFS: Clinical Frailty Scale; SB: Sedentary Behaviour.*

management[28]. Inflammation occurs due to excessive activity of the immune system, derived from antigenic epitopes and pro-inflammatory molecules, in addition to the use of therapies that trigger the regulation of immune cells, causing in some cases an innate and adaptive immunity, leading to an altered immune system[29]. The virus also has the ability to invade the brain parenchyma, endothelium, heart and alter clotting, and as a result of a weaker immune function as a result of stroke, the symptoms that manifest in these patients are major[30,31].

Previous litearture[32] has shown that the type and mainly the size of NHs (measured in the number of resident beds) influences the incidence of COVID-19 infection within NHs, as in our study. The results of our study also identified that the type of residence, in this case private, could be related to a greater probability of suffering symptomatic COVID-19, with a greater risk of severity and complications. Braun et al., (2020) attributed these results to the shortage of PPE in private NHs[33]. Around 75% of NHs in Spain are private, with around 271696 private places, compared to 101289 publicly owned resident places[34]. Studies have shown that the larger the size of the NH, the higher the

risk of death from COVID-19[35]. Inadequate infrastructure, lack of space and high occupancy of NHs at the time of the crisis increased the chances of contracting COVID-19 with more symptomatology[9]. It is important to identify those factors that are modifiable and found within the institution and the different levels of pathology transmission in NHs[36]. Nursing homes have a disproportionately high level of risk for COVID-19 transmission[37], for this reason, recording COVID-19 mortality in a NH can inform aspects of risk management and allows for optimizing care in future interventions in NHs[36].

The main limitation of this study is the small sample size; nevertheless, the pandemic outbreak in March 2020 marked the end of the baseline NHs data collection. In addition, we are uncertain about the accuracy of serologic testing in persons with mild or no symptoms[37], but this study was based on the tools used in the NHs and the existing literature at the time. A strength of the study is that baseline testing was completed just prior to the pandemic and the longitudinal design allowed data collection over a one-year period within 5 different NHs.

In terms of implications for clinical practice, it is important to provide additional protection for NH residents who have suffered a stroke since they are at increased risk for symptomatic COVID-19, particularly as many residents were COVID-19 positive but not symptomatic, to avoid cross-contamination. Now we know more about COVID-19 and its impact on NHs, social and health services should improve and tailor contingency plans to prevent the spread of infectious diseases in NHs to protect the most vulnerable and frail population segment of our society. Special attention to address environmental factors such as inadequate infrastructure, poorly ventilated environment, high occupancy and low staffing is required.

Conclusions

It can be concluded that having suffered a stroke and living permanently in a private NH represented risk factors for symptomatic COVID-19 in this sample of institutionalized older people. Over half of residents who tested positive for COVID-19 were not symptomatic and this can increase cross-contamination. A large, adequately powered study is recommended to support the results from this research.

Ethics approval

Ethical permission was obtained by the Ethics and Research Committee of the University of Vic - Central University of Catalonia (registration number 92/2019). The project meets the criteria required in the Helsinki Declaration, as well as the Organic Law 3/2018 (December 5) on the Protection of Personal Data and Guarantee of Digital Rights.

Consent to participate

Signed informed consent was gained from the resident or his/her legal guardian.

Authors' contributions

AES, EMM, JJR, DLBS; methodology, AES, EMM, JJR, SRF, PFG, MMT, DLBS, EGR; formal analysis, AES, EMM, JJR, PFG, DLBS; investigation, AES, EMM, JJR, SRF, PFG, MMT, DLBS, DAS, EGR; data curation, AES, EMM, JJR, PFG, MMT, DLBS; writing-original draft preparation, AES, EMM, JJR, SRF; writing-review and editing, AES, EMM, JJR, SRF, PFG, MMT, DLBS, DAS, EGR; supervision, EMM, JJR, DAS, DLBS. All authors have read and agreed to the published version of the manuscript.

Disclaimer

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