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RESEARCH ARTICLE

REVISED Asymptomatic COVID-19 in the elderly: dementia and viral clearance as risk factors for disease progression. [version 2; peer review: 2 approved]

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Abstract

Background:
SARS-CoV-2 infected individuals ≥60 years old have the highest hospitalization rates and represent >80% fatalities. Within this population, those in long-term facilities represent >50% of the total COVID-19 related deaths per country. Among those without symptoms, the rate of pre-symptomatic illness is unclear, and potential predictors of progression for symptom development are unknown.
Our objective was to delineate the natural evolution of asymptomatic SARS-CoV-2 infection in elders and identify determinants of progression.

Methods:
We established a medical surveillance team monitoring 63 geriatric institutions in Buenos Aires, Argentina during June-July 2020. When an index COVID-19 case emerged, we tested all other eligible asymptomatic elders ≥75 or >60 years old with at least 1 comorbidity. SARS-CoV-2 infected elders were followed for 28 days. Disease was diagnosed when any COVID-19 manifestation occurred. SARS-CoV-2 load at enrollment, shedding on day 15, and antibody responses were also studied.

Results:
After 28 days of follow-up, 74/113(65%) SARS-CoV-2-infected elders remained asymptomatic. 54% of pre-symptomatic patients developed hypoxemia and ten pre-symptomatic patients died.

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 04 Apr 2022		✓ view
version 1 27 Aug 2021	✓ view	? view

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Any reports and responses or comments on the article can be found at the end of the article.

Dementia was the only clinical risk factor associated with disease(OR 2.41(95%CI=1.08, 5.39). In a multivariable logistic regression model, dementia remained as risk factor for COVID-19 severe disease. Furthermore, dementia status showed a statistically significant different trend when assessing the cumulative probability of developing COVID-19 symptoms(log-rank p=0.027).
On day 15, SARS-CoV-2 was detectable in 30% of the asymptomatic group while in 61% of the pre-symptomatic(p=0.012).
No differences were observed among groups in RT-PCR mean cycle threshold at enrollment(p=0.391) and in the rates of antibody seropositivity(IgM and IgG against SARS-CoV-2).

Conclusions:
In summary, 2/3 of our cohort of SARS-CoV-2 infected elders from vulnerable communities in Argentina remained asymptomatic after 28 days of follow-up with high mortality among those developing symptoms. Dementia and persistent SARS-CoV-2 shedding were associated with progression from asymptomatic to symptomatic infection.

Keywords
asymptomatic, pre-symptomatic, elders, COVID-19, risk factors, dementia, geriatric institutions, long-term facilities

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REVISED **Amendments from Version 1**

In this new version of the article, we have addressed comments made by the reviewers. In detail, a multivariate analysis was added to the evaluation of potential predictors of symptom development in asymptomatic SARS-CoV-2 infected patients. After adjusting for multiple variables of interest, a significant association between dementia and the pre-symptomatic state remained.

In addition, in the multivariate logistic regression analyzing the relationship between dementia and the development of COVID-19 severe disease, more variables were added without restricting the inclusion of covariates. The association between dementia and COVID-19 severe disease also remained.

In both analyses, evaluating potential determinants for the development of COVID-19 symptoms or COVID-19 severe disease in asymptomatic patients, we added a new variable comparing the number of infected patients per geriatric institution evaluating the effect that COVID-19 crowding may have on the outcomes of interest.

Any further responses from the reviewers can be found at the end of the article

Introduction

Coronavirus disease 2019 (COVID-19) is particularly severe in the elderly[1]. SARS-CoV-2 infected individuals ≥60 years of age have the highest hospitalization rates and represent >80% fatalities[1–3]. Within this population, those who reside in long-term facilities may represent >50% of the total COVID-19 related deaths per country[4–6].

However, most infected seniors remain asymptomatic and never progress to experience severe disease. While in symptomatic COVID-19 elders, the predisposing risk factors for severe disease are already well described[2,3,7], among those without symptoms, the rate of pre-symptomatic illness is unclear, and potential predictors of progression for symptom development are unknown.

Our objective was to delineate the natural evolution of asymptomatic SARS-CoV-2 infection and identify potential determinants of progression to symptomatic illness. For this purpose, we established a prospective cohort of asymptomatic, SARS-CoV-2 infected individuals ≥60 years of age in geriatric institutions and investigated the role of baseline comorbidities, viral load on presentation, viral clearance, and antibody production in disease progression.

Methods

Study population

Our group established a medical surveillance team monitoring 63 geriatric institutions in Buenos Aires city and state between June and July 2020. When an index COVID-19 case emerged in one of these residencies, we tested all other consenting, eligible asymptomatic elders ≥60 years old for SARS-CoV-2. Participating seniors were asymptomatic individuals ≥75 years of age, or between 60–74 years with ≥1 comorbidity (hypertension, dementia, diabetes, obesity, chronic renal failure, and/or chronic obstructive pulmonary disease [COPD]).

Institutional review board approval was obtained and all patients or a responsible first-degree family member signed informed consent for their participation in the protocol (Centro de Estudios Infectológicos SA CEIC, Ethics Approval Number 1146).

Clinical monitoring

SARS-CoV-2 infected, asymptomatic elders were followed daily for 28 days by a medical team using pre-designed questionnaires. Symptoms of COVID-19 included fever (axillary temperature >37.5°C), chills, cough, tachypnea (respiratory rate >20 per minute), physician-diagnosed difficulty breathing, hypoxemia (O_2 sat<93% when breathing room air), myalgia, anorexia, sore throat, dysgeusia, anosmia, diarrhea, vomiting, and rhinorrhea. Disease was diagnosed when any of these manifestations occurred within 14 days of SARS-CoV-2 detection (95% of symptomatic patients) or between 15 and 28 days of persistently positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) results with no other clinical possible explanation. COVID-19 severe disease was defined as oxygen requirement due to hypoxemia. SARS-CoV-2 load at enrollment, shedding on day 15, and antibody responses at the end of study participation were also studied.

SARS-CoV-2 and antibody testing

SARS-CoV-2 was assayed in nasopharyngeal and oropharyngeal swabs following Center for Disease Control guidelines at enrollment and day 15 of diagnosis[8]**.** Samples were stored in 2 ml of normal saline and tested in duplicate by RT-PCR for SARS-CoV-2 (Atila iAMP® COVID-19).

Antibodies were assayed in 10µl of blood using a validated rapid antibody test (monoclonal immunoglobulin M (IgM) and immunoglobulin G (IgG) against SARS-CoV-2 nucleocapsid protein, SD Biosensor®, Korea) 28 days after enrollment because the test's sensitivity is reported to be higher at 4–5 weeks[9,10]. The assay was performed according to the manufacturer´s protocol[11].

Statistical analysis

Baseline comorbidities were reported using descriptive statistics. Differences between asymptomatic and pre-symptomatic participants were initially compared using the Student t-test and Chi-squared test, where appropriate. We used univariable and multivariable logistic regression to study for potential determinants for the outcomes of interest. A $p \leq 0.05$ was considered statistically significant. Progression to symptomatic illness was assessed using the Kaplan-Meier method, with any COVID-19 related symptom as outcome. Stata/SE 13 package for IBM-PC (Stata Corp) was used for analysis and R Core Team (2019) for Figures.

Results

Study Population and clinical evolution

Fourteen of 63 (22%) senior homes presented a positive, symptomatic index case during the study period. In these residencies, we swabbed 258 asymptomatic individuals between June 8 and July 3, 2020. 113 out of the 258 asymptomatic evaluated elderlies had a positive SARS-CoV-2 test and participated in the

study. Of these, 100/113 were ≥75 years of age, and 13/113 were between 60–74 years with ≥1 comorbidity (Table 1).

Participants' median age was 87 years (IQR 11.85). 93/113 (82%) were females, 98 (87%) had ≥1 comorbidity (Table 1). After 28 days of follow-up, 74 (65%) elders remained asymptomatic. In 39 (35%) pre-symptomatic patients, the median time to onset of symptoms was 3 days (IQR 6) (Figure 1). The most frequent presenting symptoms were difficulty breathing (39%), cough (37%), fever (29%), and tachypnea (16%). 21/39 (54%) pre-symptomatic patients developed hypoxemia [21/113 (19%) in the population], a presenting sign in 11/21 (52%). Median time to oxygen supplementation was 4 days (IQR 6); median duration of O2 supplementation in survivors, 4 days (IQR 5). Ten pre-symptomatic patients died (median day 13.5, IQR 12).

Risk factors for disease progression

None of the baseline conditions classically related to disease severity was associated with symptomatic illness (Table 1). Dementia was the only clinical risk factor associated with disease in a univariate logistic regression (OR 2.41 (95% CI =1.08, 5.39), p=0.03; Table 1) when compared to the asymptomatic patients. These results, with dementia as a potential predictor for the development of symptoms in our population, remained stable in a multivariate logistic regression including most frequent covariates present in our cohort (dementia, OR 2.4 (95% CI =1, 5.8), p=0.05; Table 1).

Analyzing potential predictors for COVID-19 severe disease in a multivariable logistic regression model, dementia persisted as a risk factor associated with the outcome (OR 3.42 (95% CI =1.1, 10.63), p=0.033) (Table 2). Furthermore, when assessing the cumulative probability of developing COVID-19 symptoms stratified by dementia diagnosis, it showed a statistically significant different trend in both groups (log-rank p=0.027) (Figure 2).

SARS-CoV-2 viral load and RT-PCR retesting

RT-PCR mean cycle threshold showed no differences among groups at the time of enrollment (p=0.391), with a mean of 14.65 (SD 10.13) in the asymptomatic group and a mean of 12.79 (SD 6.08) in the pre-symptomatic patients (Figure 3).

When performing a second RT-PCR testing on day 15 (IQR 1), SARS-CoV-2 was detectable in 30% (14/46) of the

Table 1. Determinants of pre-symptomatic COVID-19.

			Univariate analysis		Multivariate analysis	
	Asymptomatic (N=74)	Pre-symptomatic (N=39)	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Clinical and laboratory						
Median age (IQR) - yr	87.7 (11.57)	86.6 (13.7)	0.99 (0.99-1.00)	0.276	0.96 (0.91-1.01)	0.141
Male, no. (%)	14 (19)	6 (16)	0·78 (0.27-2.22)	0.64	0.64 (0.18-2.22)	0.482
Smoking history, no. (%)	18 (25)	12 (33)	1.47 (0.61-3.53)	0.386	1.15 (0.44-3)	0.78
Dementia, no. (%)	28 (39)	23 (61)	2.41 (1.08-5.39)	0.032	2.4 (1-5.8)	0.05
Hypertension, no. (%)	32 (43)	15 (39)	0.82 (0.37-1.81)	0.624	0.9 (0.37-2.22)	0.824
Diabetes, no. (%)	12 (16)	4 (10)	0.59 (0.18-1.97)	0.392	0.3 (0.07-1.34)	0.115
Cardiovascular disease, no. (%)	15 (20)	8 (20)	1.02 (0.39-2.66)	0.976	1.15 (0.4-3.32)	0.794
Geriatric institutions with ≥ 5 SARS-CoV-2 cases, no. (%)	64 (87)	31 (80)	0.61 (0.22-1.69)	0.337	0.48 (0.16-1.46)	0.196
Obesity, no. (%)	4 (5)	4 (10)	2 (0.47-8.48)	0.347		
Cancer, no. (%)	4 (5)	3 (8)	1.46 (0.31-6.87)	0.633		
Chronic liver disease, no. (%)	1 (1)	1 (3)	1.92 (0.12-31.57)	0.648		
End-stage renal disease, no. (%)	-	2 (5)	-	-		
Asthma, no. (%)	-	2 (5)	-	-		
Chronic obstructive pulmonary disease, no. (%)	-	3 (8)	-	-		

OR= Odds Ratio, CI = confidence interval.

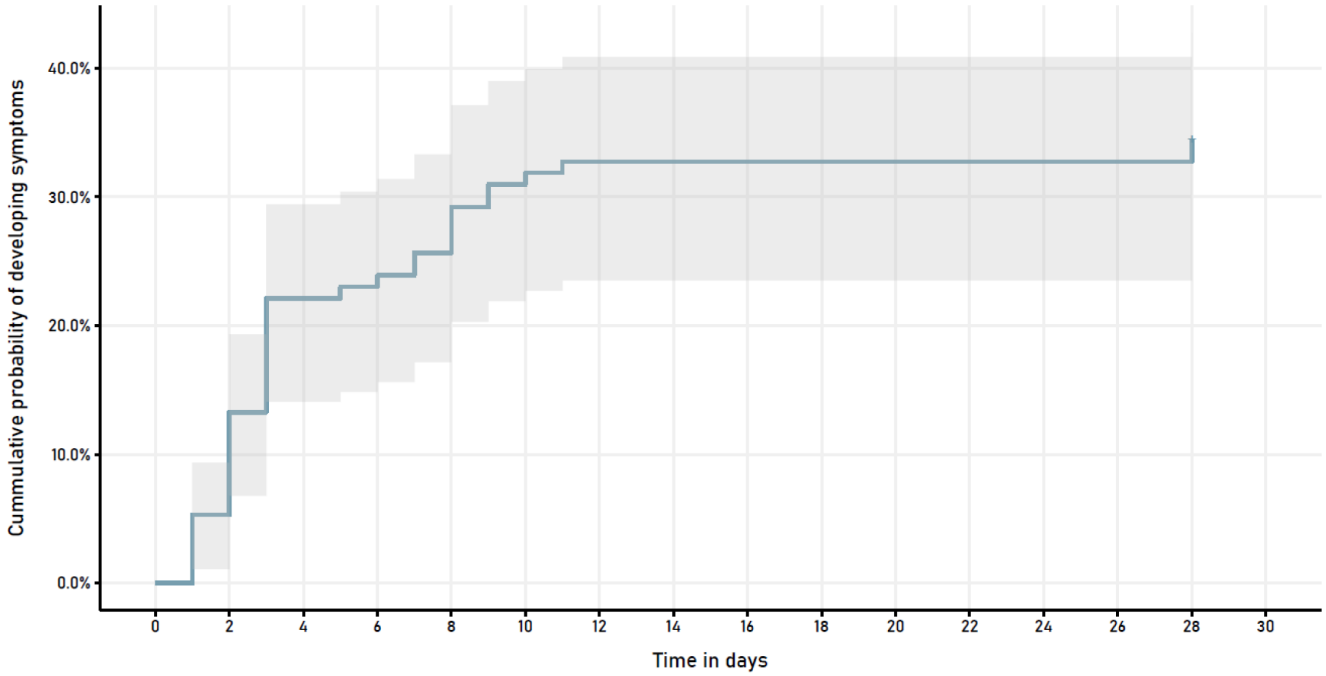

Figure 1. Symptom development in patients who were asymptomatic at time of COVID-19 diagnosis.

Table 2. Potential determinants of COVID-19 severe disease.

	Univariate analysis			Multivariate analysis		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Diabetes	0.26	0.03-2.06	0.2	0.18	0.02-1.95	0.159
Cancer	3.67	0.75-17.81	0.107	6.11	0.99-37.49	0.051
Dementia	2.81	1.03-7.64	0.043	3.42	1.1-10.63	0.033
Age	1	0.99-1	0.935	1.02	0.95-1.1	0.635
Male	1.6	0.51-5.02	0.419	2.71	0.65-11.29	0.17
Smoking history	1.79	0.66-4.89	0.256	1.16	0.35-3.84	0.805
Hypertension	0.65	0.24-1.76	0.397	0.54	0.16-1.77	0.307
Cardiovascular disease	1.76	0.6-5.21	0.304	2.16	0.61-7.71	0.235
Obesity	1.51	0.28-8.06	0.63	2.52	0.32-19.69	0.378
Geriatric institutions with ≥ 5 SARS-CoV-2 cases	0.76	0.22-2.61	0.67	0.57	0.14-2.35	0.434

OR= Odds Ratio, CI = confidence interval

asymptomatic subjects, while still present in 61% (17/28) of the pre-symptomatic patients (p=0.012).

Antibody seropositivity against SARS-CoV-2

All patients were invited to be tested for IgM and IgG against SARS-CoV-2 nucleocapsid protein four weeks after diagnosis. Seventy-six % (77/102) of those alive on day 28th of follow-up were assayed with a median day at testing of 28 (IQR 3).

No differences were observed in the rates of antibody seropositivity between asymptomatic and pre-symptomatic patients

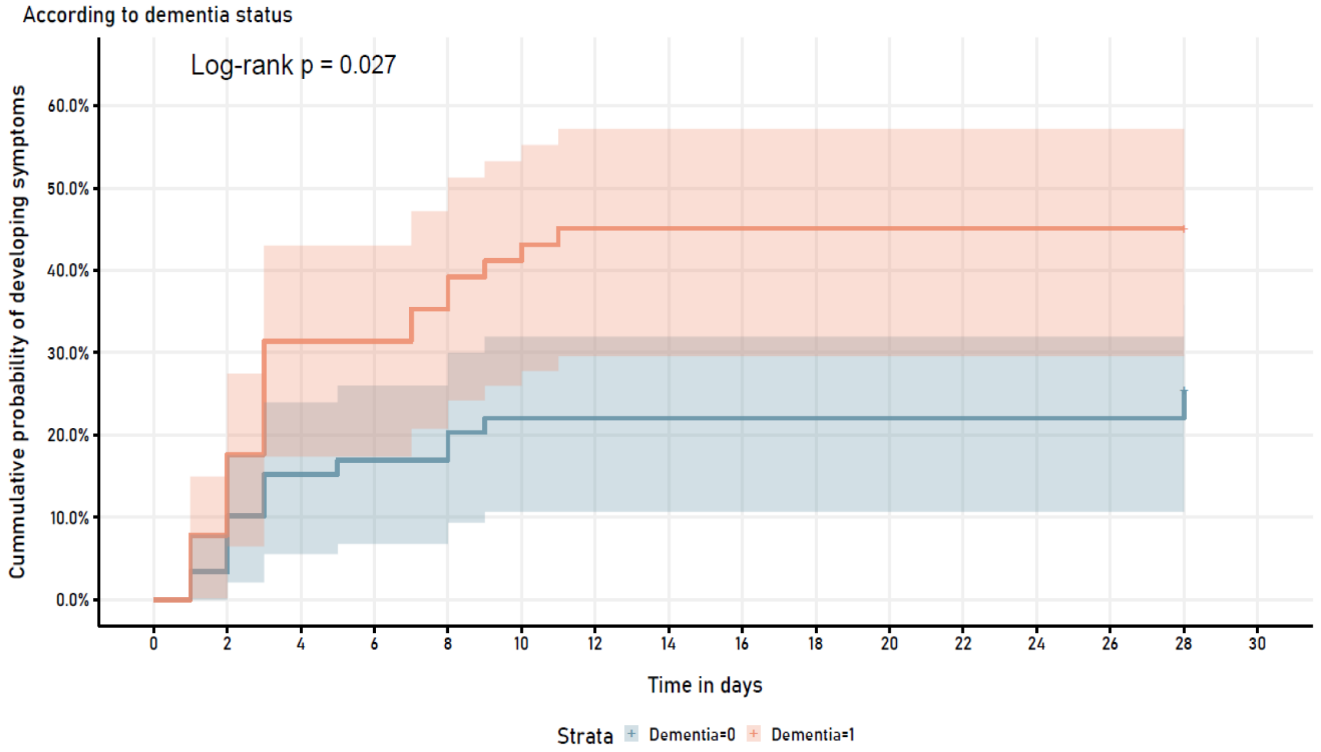

Figure 2. **Symptom development in patients who were asymptomatic at time of COVID-19 diagnosis.**

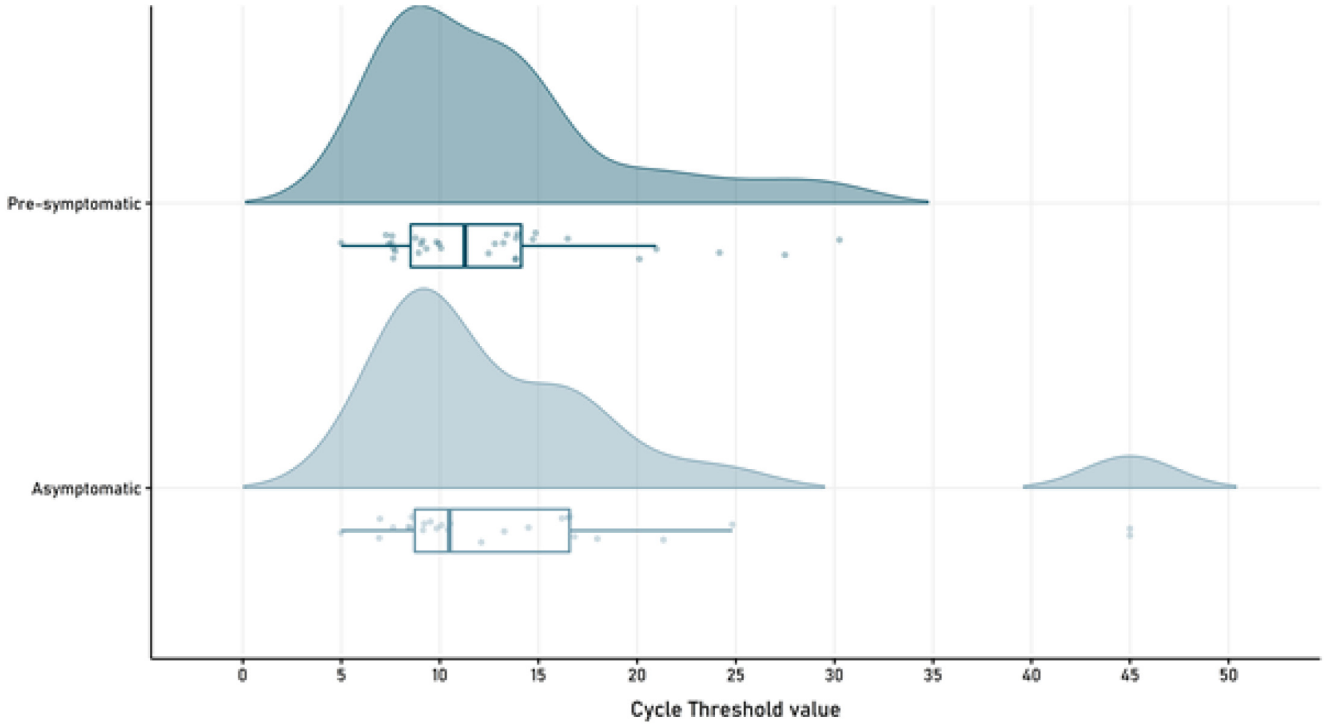

Figure 3. **SARS-CoV-2 cycle threshold value in pre-symptomatic and asymptomatic patients.**

respectively (IgM+: 53% (31/59) vs 56% (10/18), p=0.823) (IgG+: 83% (49/59) vs 83% (15/18), p=0.978).

Discussion

Early recognition of asymptomatic infected patients and defining the determinants of progression from asymptomatic to symptomatic illness in the elderly are critical to examine potential disease-sparing interventions. However, since asymptomatic patients usually do not seek medical assistance or COVID-19 testing, this represents a great challenge.

In our cohort, 35% aged study participants remained asymptomatic, only 19% developed an oxygen requirement and 9% of all patients died due to COVID-19. Asymptomatic SARS-CoV-2 infected patients play a paramount role in the pandemic, both as sources of viral spreading and as at-risk subjects for hospitalization. Interestingly, few studies examined them in detail[12]. On the Diamond Princess cruise ship, 88% of asymptomatic and relatively younger patients (median=59.5 years) did not progress to disease[13] while, in skilled nursing facilities in the U.S. and in line with our observations, 68% failed to develop illness[14]. Our case-fatality ratio in symptomatic patients (26%, 10/39), is considerably higher than the one described in Argentina and worldwide[15]. This emphasizes the relevance of the population under study (residents of long-term facilities), given their high susceptibility for COVID-19 severe disease[4–6].

Dementia was the sole baseline difference potentially predicting progression to symptomatic disease in our study. Our findings suggest that cognitive impairment plays a key role in disease inception and disease progression in the elderly. Other comorbidities associated with progression from mild to severe symptoms[2,16] did not affect the odds of experiencing pre-symptomatic illness in this population. Furthermore, dementia at baseline was strongly associated with those requiring oxygen. Cognitive impairment has been previously identified in Britain as a risk factor for hospitalization in older patients (OR 3.5 (95% CI =1.93, 6.34))[17]. However, our study is the first to prospectively identify dementia as a risk factor for pre-symptomatic illness. There are different reasons behind the elevated mortality seen in long-term facilities worldwide and in our study, that may also explain the role of dementia and cognitive impairment in COVID-19 disease progression. To begin with, residents in geriatric institutions are in close contact with numerous healthcare workers with a consequent increased risk for contracting SARS-CoV-2 infection[6]. In addition, patients with cognitive impairment may present difficulties in carrying out isolation and the physical distancing needed. Furthermore, patients with dementia were described to present particularly higher blood levels of urea, white blood cell count, and an association with neurological consequences of COVID-19[6,18]. Other participants baseline characteristics that could also potentially explain the relationship between dementia and the development of COVID-19 related symptoms are nutrition status, the level of exercise and clinical frailty scale.

No difference in viral load in respiratory secretions was evident at diagnosis between groups, in line with previous reports[19–21]. But two weeks after enrollment, the pre-symptomatic group doubled the asymptomatic subjects in the persistence of SARS-CoV-2 detection in respiratory secretions. This longer viral shedding associated with evolution to symptomatic disease, suggests that control of viral replication may influence symptom inception. In line with our findings, infectivity may be weaker in asymptomatic elders than in those fully developing symptoms[22]. A recent study showed similar results in PCR retesting in SARS-CoV-2 asymptomatic and symptomatic patients, and interestingly, this could be evidenced during the first week after diagnosis[23].

Antibody diagnostics tests are critical for detecting asymptomatic patients[24]. IgM antibodies peak 4 for days after onset of symptoms, declining to become undetectable after 4 weeks. Whereas IgG reaches detectable levels at day 7 and remains highly elevated until 8 months of diagnosis even in asymptomatic patients[25–27]. Interestingly, Grossberg *et al.* showed that symptomatic individuals experience a different immune response than asymptomatic SARS-CoV-2 infected patients, revealed by higher levels of IgG against spike 1 and 2 glycoprotein, receptor-binding domain (RBD), and nucleoprotein. While asymptomatic patients may present a more robust IgM response[28].

Nevertheless, IgM and IgG responses were similar with and without symptoms in our cohort, findings aligned with their preventive role in early stages after or even before infection but their lesser influence once disease course has been established[29].

Our study has limitations. First of all, older adults, and in particular those with cognitive impairment may present greater difficulties in referring their symptoms. However, all patients were under strictly daily control by nurses and the institution's medical team that accurately reported all symptoms and signs presented. In addition, while no difference was seen among groups in the IgM and IgG levels against SARS-CoV-2 nucleocapsid protein, a more complex analysis of the immune response including neutralizing antibodies, and antibodies titers against spike glycoproteins and RBD, may elucidate differences between groups. Moreover, to further strengthen this study, a cross-validation technique should be used to evaluate the effectiveness of this predictive model. Also, the role of dementia in SARS-CoV-2 infected elderlies should be evaluated in a cohort with a different prevalence of comorbidities.

In summary, we present a cohort of SARS-CoV-2 infected elders from vulnerable communities in Argentina, where 2/3 of them remained asymptomatic after 28 days of follow-up with high mortality among those developing symptoms. Dementia and persistent SARS-CoV-2 shedding were associated with progression from asymptomatic to symptomatic infection. Evidently, COVID-19 risk control and prevention are imperative in this high-risk population. These observations may alter

our thinking of SARS-CoV-2 asymptomatic infection in the elderly, and if confirmed in other studies, require us to include patients with dementia as candidates for prevention strategies.

Data availability

Figshare. "Asymptomatic COVID-19 in the elderly: dementia and viral clearance as risk factors for disease progression". SAS Dataset. DOI: https://doi.org/10.6084/m9.figshare.15050217.v1[30]

Figshare. "Asymptomatic COVID-19 in the elderly: dementia and viral clearance as risk factors for disease progression". Stata dataset. DOI: https://doi.org/10.6084/m9.figshare.15050223.v1[31]

Figshare. "Asymptomatic COVID-19 in the elderly: dementia and viral clearance as risk factors for disease progression". Stata Dofile. DOI: https://doi.org/10.6084/m9.figshare.15050220.v1[32]

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Reviewer Report 06 April 2022

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✔ **Kirsten E. Wiens**
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

The authors have addressed my comments and I have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 16 February 2022

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? **Kirsten E. Wiens**
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

In this paper, Esteban *et al.* conduct a prospective study of 113 SARS-CoV-2-infected elderly adults in 13 senior homes in Buenos Aires during June-July 2020. They follow the study participants over

28 days, monitoring symptoms, viral load, and IgM/IgG responses to SARS-CoV-2 nucleocapsid. They find that the only risk factor significantly associated with developing symptoms following infection was dementia.

This is an important paper, and one of its strengths is that the study team prospectively monitored 63 senior homes in Buenos Aires for symptomatic index cases in order to identify participants for inclusion, allowing them to actively recruit asymptomatically infected individuals whether or not they sought testing. There are also a few components of the analysis and discussion of the results that could be improved:

1. Throughout the manuscript, I'd suggest being careful with the use of the terms "determinants" and "was predictive of". The authors have shown that dementia is strongly associated with increased risk of developing symptoms among the elderly, but they don't actually test how good the different risk factors are in prediction (e.g., through cross-validation).

2. It would be helpful to have further discussion and/or analysis of additional variables that may be associated with symptoms. For example, were there differences in severity or extent of outbreaks in the senior homes (which might impact viral dose or number of exposures)? If so, these could be examined in the regression models and/or senior home could be included as a random effect. Various other individual-level factors may impact severity (nutrition, past infection, exercise, etc), which the authors may not be able to evaluate, but could discuss.

3. Why was the multivariable logistic regression only run for severe COVID-19 disease, rather than for asymptomatic vs. pre-symptomatic? For consistency with the rest of the paper, I think it's important to include this analysis for symptomatic disease.

4. Why was a p value of 0.2 used to select covariates in the multivariable logistic regression? What happened if you put all the covariates in? Or just remove highly collinear covariates?

Minor comments:

- I suggest including the study location (Bueno Aires, Argentina) and dates (June-July 2020) in the methods of the abstract.

- 258 asymptomatic individuals were swabbed and 113 asymptomatic SARS-CoV-2 infected individuals were included. How many of the 258 were positive but declined to participate or were lost to follow-up?

- Dementia was also the most common comorbidity in this cohort. The authors might speculate on whether their findings may be different in larger cohorts or populations where risk factors such as obesity or cancer are more common.

- In the first sentence of the discussion, I'd use percentages rather than fractions (so that those denominators don't get confused with sample sizes).

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Mar 2022

Ignacio Esteban, INFANT Foundation, Buenos Aires, Argentina

Response to Reviewer 2:

In this paper, Esteban et al. conduct a prospective study of 113 SARS-CoV-2-infected elderly adults in 13 senior homes in Buenos Aires during June-July 2020. They follow the study participants over 28 days, monitoring symptoms, viral load, and IgM/IgG responses to SARS-CoV-2 nucleocapsid. They find that the only risk factor significantly associated with developing symptoms following infection was dementia.

This is an important paper, and one of its strengths is that the study team prospectively monitored 63 senior homes in Buenos Aires for symptomatic index cases in order to identify participants for inclusion, allowing them to actively recruit asymptomatically infected individuals whether or not they sought testing. There are also a few components of the analysis and discussion of the results that could be improved:

We greatly appreciate Reviewer 2's perspective and input. We have made modifications to the article addressing these topics. Please find specific comments to each commentary below.

- Throughout the manuscript, I'd suggest being careful with the use of the terms "determinants" and "was predictive of". The authors have shown that dementia is strongly associated with increased risk of developing symptoms among the elderly,

but they don't actually test how good the different risk factors are in prediction (e.g., through cross-validation).

We thank the reviewer for this comment. We have addressed this through the article accordingly. In addition, we have added it as a study limitation in the discussion section.

- It would be helpful to have further discussion and/or analysis of additional variables that may be associated with symptoms. For example, were there differences in severity or extent of outbreaks in the senior homes (which might impact viral dose or number of exposures)? If so, these could be examined in the regression models and/or senior homes could be included as a random effect. Various other individual-level factors may impact severity (nutrition, past infection, exercise, etc), which the authors may not be able to evaluate but could discuss.

The reviewer is correct. There are other variables such as nutrition status, exercise, and frailty that could also explain the effect of dementia on the development of symptoms and COVID-19 severe disease. We have addressed these now in our discussion section since data for those variables was not available at the time. None of the participants were previously infected with SARS-CoV-2.
To evaluate the potential effect of the number of infected patients per senior home we included a new variable according to the distribution of our participants in each senior home to compare this, which showed no association with the outcomes nor confounding on the relationship between dementia and the outcomes of interest. This information was now added to the results section, Table I and Table II, and is now available in the updated dataset.

- Why was the multivariable logistic regression only run for severe COVID-19 disease, rather than for asymptomatic vs. pre-symptomatic? For consistency with the rest of the paper, I think it's important to include this analysis for symptomatic disease.

We thank the reviewer for this comment since we agree it is key for the correct interpretation of the results. For the first analysis, seeking for potential determinants associated with the status pre-symptomatic we only ran a univariate analysis since as we mentioned in the Statistical Analysis section and the reviewer in her next comment, we only selected co-variates with a p-value <=0.2 on univariate analysis. Given our sample size and the number of events per outcome (pre-symptomatic disease = 39, COVID-19 severe disease = 21) we selected this previously validated strategy to conduct a purposeful selection of covariates [1,2]. Given that none of the studied co-variates reached this threshold we did not conduct a multivariable analysis for this outcome.
Nevertheless, we agree a multivariate analysis may strengthen our analysis and we thank the reviewer for this comment. We have now added this new information, a multivariate analysis in table I and in the Results section.

- Why was a p value of 0.2 used to select covariates in the multivariable logistic regression? What happened if you put all the covariates in? Or just remove highly collinear covariates?

As per the comment above, we have now added all of the discussed variables to the multivariable analysis where the potential association between dementia and COVID-19 severe disease remained (please find this in the Results section and in Table II).

Minor comments:

- I suggest including the study location (Bueno Aires, Argentina) and dates (June-July 2020) in the methods of the abstract.

We have now added this information to the abstract.

- 258 asymptomatic individuals were swabbed and 113 asymptomatic SARS-CoV-2 infected individuals were included. How many of the 258 were positive but declined to participate or were lost to follow-up?

All of the participants with a positive result on the nasal swab accepted to participate in the study. The remaining 145 participants that were not included in the study had a negative COVID-19 test. We have clarified this information in the Results section. None of the patients was classified as loss to follow-up, due to the established surveillance strategy, the size of our cohort, and the follow-up time.

- Dementia was also the most common comorbidity in this cohort. The authors might speculate on whether their findings may be different in larger cohorts or populations where risk factors such as obesity or cancer are more common.

The reviewer is correct. We have addressed this now in the Discussion section.

- In the first sentence of the discussion, I'd use percentages rather than fractions (so that those denominators don't get confused with sample sizes).

We thank the reviewer for this comment. We have modified this sentence in the Discussion section.

References:

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Competing Interests: None to declare.

Reviewer Report 06 October 2021

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Carlota Dobaño
ISGlobal, Hospital Clínic, University of Barcelona, Barcelona, Spain

The article by Esteban *et al.* presents a longitudinal study in long-term geriatric facilities to evaluate the proportion of individuals with asymptomatic vs symptomatic SARS-CoV-2 infection and the risk factors for negative disease progression and mortality in Argentina. Data from multivariable models indicate that dementia and persisting viral shedding were associated with negative outcomes in the elderly. This is a well done and valuable study to better understand the rate of pre-symptomatic illness and prognosis of COVID-19 when still asymptomatic, in one of the most vulnerable populations in an urban environment.

Some comments:

- "those in long-term facilities represent >50% of the total COVID-19 related deaths per country." Indicate what country or what type of countries as this may not be universal worldwide.

- Among limitations, it could be that the other comorbidities studied that were not significant predictors could have a role in larger studies (hypertension, diabetes, obesity, chronic renal failure, COPD). Please discuss.

- Antibody data was only analyzed as categorical variable (seropositive-seronegative) with rapid tests, but there could be a value to look into magnitude of response in relation to outcomes. Did authors attempt this analysis or do they have samples stored for antibody or biomarker analyses?. As indicated, "a more complex analysis of the immune response including neutralizing antibodies, and antibodies titers against spike glycoproteins and RBD, may elucidate differences between groups."

- For interpretation: the finding that dementia was associated with negative disease progression. Beyond cognitive impairment, distancing, urea and FBC that are mentioned. Since the physiological causes of dementia are not fully understood, could there be immunological basis that might be shared with mechanisms that have been linked to severe COVID-19? (e.g. immune senescence and unbalanced inflammation phenomena). Could some discussion elude to this option?

- Similarly, the inability to control the virus in the mucosa (persistent PCR+ being also associated with outcomes) could be linked to immunological dysfunction in those patients? This could also be briefly discussed.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology, vaccines, infectious diseases, global health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.