



RESEARCH ARTICLE

Asymptomatic COVID-19 in the elderly: dementia and viral clearance as risk factors for disease progression. [version 1; peer review: awaiting peer review]

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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. 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. 21/39(54%) pre-symptomatic patients developed hypoxemia and ten pre-symptomatic patients died (median day 13.5, IQR 12).

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 a 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 nucleocapsid protein).

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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Introduction

Coronavirus disease 2019 (COVID-19) is particularly severe in the elderly¹. SARS-CoV-2 infected individuals ≥ 60 years of age have the highest hospitalization rates and represent $>80\%$ fatalities¹⁻³. Within this population, those who reside in long-term facilities may represent $>50\%$ of the total COVID-19 related deaths per country⁴⁻⁶.

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 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 $>37.5^\circ\text{C}$), 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 diagnosis⁸. 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 10 μl 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 protocol¹¹.

Statistical analysis

Baseline comorbidities were reported using descriptive statistics. Differences between asymptomatic and pre-symptomatic participants were compared using the Student t-test and Chi-squared test, where appropriate. Variables with a p-value ≤ 0.2 were defined as candidates for multivariable evaluation. A $p < 0.05$ 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

Thirteen of 63 (20%) 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 asymptomatic SARS-CoV-2-infected elderly 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

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

	Asymptomatic (N=75)	Pre-symptomatic (N=38)	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)	0.277*
Male, no. (%)	14 (19)	6 (16)	0.78 (0.27-2.22)	0.64**
Smoking history, no. (%)	18 (25)	12 (33)	1.47 (0.61-3.53)	0.385**
Dementia, no. (%)	28 (39)	23 (61)	2.41 (1.08-5.39)	0.03**
Hypertension, no. (%)	32 (43)	15 (39)	0.82 (0.37-1.81)	0.624**
Diabetes, no. (%)	12 (16)	4 (10)	0.59 (0.18-1.97)	0.388**
Cardiovascular disease, no. (%)	15 (20)	8 (20)	1.02 (0.39-2.66)	0.976**
Obesity, no. (%)	4 (5)	4 (10)	2 (0.47-8.48)	0.339**
Cancer, no. (%)	4 (5)	3 (8)	1.46 (0.31-6.87)	0.632**
Chronic liver disease, no. (%)	1 (1)	1 (3)	1.92 (0.12-31.57)	0.642**
End-stage renal disease, no. (%)	-	2 (5)	-	-
Asthma, no. (%)	-	2 (5)	-	-
Chronic obstructive pulmonary disease, no. (%)	-	3 (8)	-	-

OR= Odds Ratio, CI = confidence interval, * Student t test, ** Chi-squared test

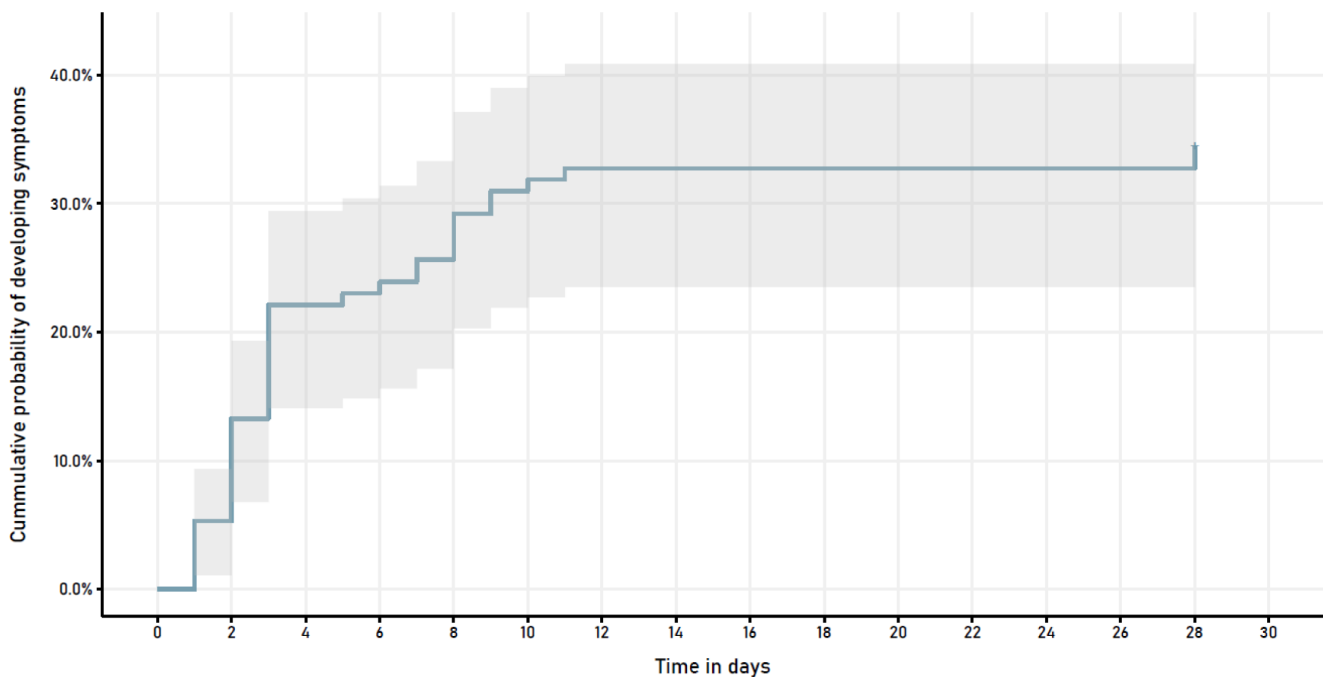


Figure 1. Symptom development in patients who were asymptomatic at time of COVID-19 diagnosis.

disease (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 univariate logistic regression (dementia, p=0.032).

Analyzing potential predictors for COVID-19 severe disease in a multivariable logistic regression model, including variables with a p-value <=0.2 in univariate analysis (cancer history and diabetes), dementia persisted as a risk factor associated with the outcome (OR 3.02 (95% CI =1.08, 8.45), p=0.035) (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 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 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, 2/3 aged study participants remained asymptomatic, only 1/5 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 detail¹². On the Diamond Princess cruise ship, 88% of asymptomatic and relatively younger patients (median=59.5 years) did not progress to disease¹³ while, in skilled nursing facilities in the U.S. and in line with our observations, 68% failed to develop illness¹⁴. Our case-fatality ratio in symptomatic patients (26%, 10/39), is considerably higher than the one described in Argentina and worldwide¹⁵. This emphasizes the relevance of the population under study (residents of long-term facilities), given their high susceptibility for COVID-19 severe disease⁴⁻⁶.

Table 2. 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	0.23	0.03-1.9	0.173
Cancer	3.67	0.75-17.81	0.107	4	0.73-21.82	0.11
Dementia	2.81	1.03-7.64	0.043	3.02	1.08-8.45	0.035
Age	1	0.99-1	0.935			
Male	1.6	0.51-5.02	0.419			
Smoking history	1.79	0.66-4.89	0.256			
Hypertension	0.65	0.24-1.76	0.397			
Cardiovascular disease	1.76	0.6-5.21	0.304			
Obesity	1.51	0.28-8.06	0.63			

OR= Odds Ratio, CI = confidence interval

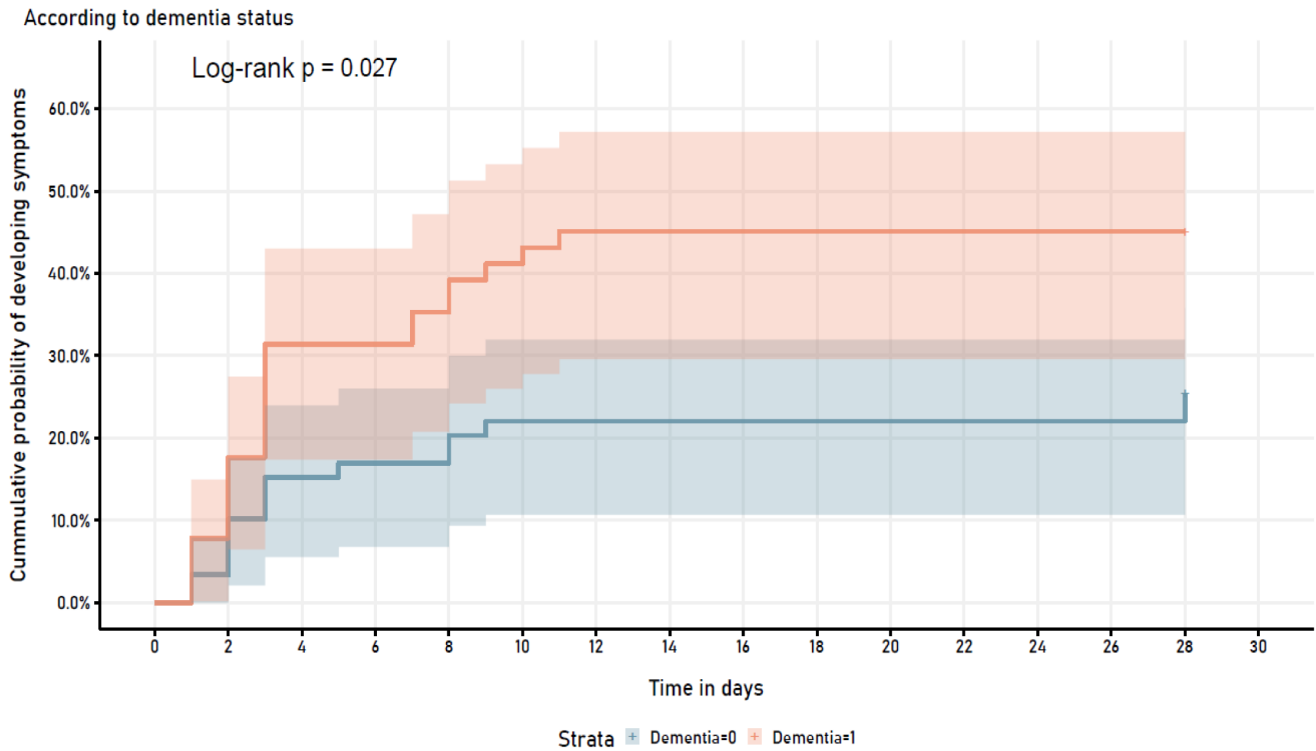


Figure 2. Symptom development in patients who were asymptomatic at time of COVID-19 diagnosis.

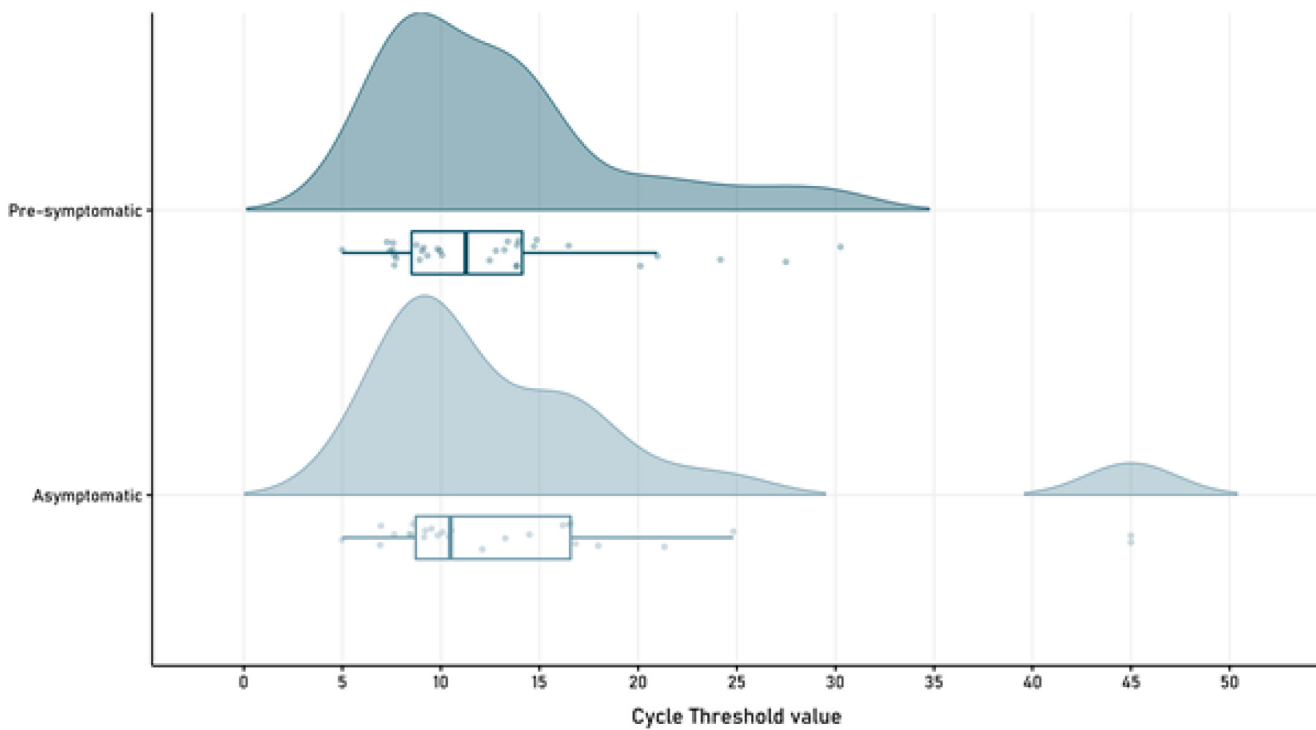


Figure 3. SARS-CoV-2 cycle threshold value in pre-symptomatic and asymptomatic patients.

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 successfully predicted 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 infection⁶. 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}.

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 symptoms²². 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 diagnosis²³.

Antibody diagnostics tests are critical for detecting asymptomatic patients²⁴. 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 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 response²⁸.

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 established²⁹.

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.

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](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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