Atypical symptoms, SARS-CoV-2 test results and immunisation rates in 456 residents from eight nursing homes facing a COVID-19 outbreak

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Abstract

Background: Frail older persons may have an atypical presentation of coronavirus disease 2019 (COVID-19). The value of real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) testing for identifying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nursing homes (NHs) residents is not known.

Objective: To determine whether (i) atypical symptoms may predict rRT-PCR results and (ii) rRT-PCR results may predict immunisation against SARS-CoV-2 in NH residents.

Design: A retrospective longitudinal study.

Setting: Eight NHs with at least 10 rRT-PCR-positive residents.

Subjects: A total of 456 residents.

Methods: Typical and atypical symptoms recorded in residents' files during the 14 days before and after rRT-PCR testing were analysed. Residents underwent blood testing for IgG-SARS-CoV-2 nucleocapsid protein 6 to 8 weeks after testing. Univariate and multivariate analyses compared symptoms and immunisation rates in rRT-PCR-positive and negative residents.

Results: A total of 161 residents had a positive rRT-PCR (35.3%), 17.4% of whom were asymptomatic before testing. Temperature >37.8°C, oxygen saturation <90%, unexplained anorexia, behavioural change, exhaustion, malaise and falls before testing were independent predictors of a further positive rRT-PCR. Among the rRT-PCR-positive residents, 95.2% developed SARS-CoV-2 antibodies vs 7.6% in the rRT-PCR-negative residents. Among the residents with a negative rRT-PCR, those who developed SARS-CoV-2 antibodies more often had typical or atypical symptoms (P = 0.02 and <0.01, respectively).

Conclusion: This study supports a strategy based on (i) testing residents with typical or unexplained atypical symptoms for an early identification of the first SARS-CoV-2 cases, (ii) rRT-PCR testing for identifying COVID-19 residents, (iii) repeated wide-facility testing (including asymptomatic cases) as soon as a resident is tested positive for SARS-CoV-2 and (iv) implementing SARS-CoV-2 infection control measures in rRT-PCR-negative residents when they have unexplained typical or atypical symptoms.
Keywords: COVID-19, testing for SARS-CoV-2, nursing homes, rRT-PCR, symptoms, antibodies, immunisation, older people

Key Points
• Anorexia, behavioural change, exhaustion, malaise and falls are possible COVID-19 symptoms in nursing home residents.
• Positive and negative predictive values of SARS-CoV-2 immunisation by rRT-PCR are 95.2 and 92.4% in nursing home residents. 61% of residents tested negative by rRT-PCR who developed SARS-CoV-2 immunisation had symptoms consistent with COVID-10.

Introduction
Nursing home (NH) residents represent more than one-third of coronavirus disease 2019 (COVID-19)-related deaths in the Western countries. NHi s are closed environments that are very conducive to outbreaks. Their residents are extremely vulnerable to severe forms of COVID-19, with a mortality rate exceeding 25% [1–3]. The strategy used to prevent COVID-19 outbreaks in NHs was initially based on: (i) a daily screening of symptoms consistent with COVID-19 in residents, staff members and visitors, (ii) nasopharyngeal testing using the real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in symptomatic subjects and (iii) the implementation of appropriate infection prevention and control measures [4–6]. In an NH facing a COVID-19 outbreak, over half of the rRT-PCR-positive residents were asymptomatic at the time of testing [7]. This major finding led to the addition of the following recommendation: rRT-PCR testing of all residents, including the asymptomatic ones, for all new identified cases, and repeat testing until no new cases are identified [5,6].

The high percentage of asymptomatic rRT-PCR-positive residents found in Aron’s study [7] may have been overestimated, since some atypical symptoms, further attributed to COVID-19 in frail older people [8–20], were not considered. It is also possible that some of the symptomatic residents with repeated negative rRT-PCR test results for SARS-CoV-2 may have developed antibodies a few weeks later.

In March 2020, the Health Agency of the French Occitanie region recommended the following: (i) to make a daily report of any unusual and unexplained symptoms in the NH residents’ files, (ii) to perform an rRT-PCR test in residents presenting unusual symptoms without any obvious cause, (iii) to perform an rRT-PCR test on all residents, including those asymptomatic, in the case of a positive test result in a resident, (iv) to repeat testing in all residents tested negative once every 7 days until no new cases were identified for at least 14 days and (v) to implement appropriate infection prevention and control measures in residents with positive rRT-PCR testing or with unexplained symptoms, even if repeated testing was negative [21]. COVID-19 support platforms were concomitantly set up in proximity hospitals to help NHs to follow regional guidance [22]. In May 2020, the same Agency recommended to perform SARS-CoV-2 serology in residents of NHs having faced a COVID-19 outbreak in order to better prepare for a new outbreak.

The objectives of this study, conducted in NHs facing a COVID-19 outbreak, were to determine (i) the phenotype of rRT-PCR-positive and negative residents, (ii) whether typical and atypical symptoms differ between rRT-PCR-positive and negative residents and (iii) how well rRT-PCR testing results can predict immunisation against SARS-CoV-2 in NH residents.

Methods
Design of the study
A retrospective longitudinal study was carried out in NHs having faced a SARS-CoV-2 outbreak in the Occitanie region between 3 March and 10 June 2020. This analysis was based on symptoms prospectively recorded by doctors or nurses in the residents’ files, in accordance with the Occitanie Health Agency guidance.

Setting
NHs reporting 10 or more residents with a positive rRT-PCR result in the Occitanie region (Appendix 1).

Participants
As soon as COVID-19 was diagnosed in at least one NH resident, all residents and/or their relatives were informed of the regional guidance to reduce SARS-CoV-2 dissemination in NHs. When the COVID-19 outbreak was controlled in the NH, all residents and/or their relatives were informed that the residents’ anonymized clinical and biological data would be used for research purposes. None of them disagreed. This study was approved by the Institutional Review Board of the Montpellier hospital (IRB-MTP_2020_06_202000534).

Outcomes
The symptoms noted by the doctors or nurses in the residents’ medical files (by using their usual medical information intelligence software) were retrospectively analysed by two doctors who were not aware of the rRT-PCR and blood test
results. Recorded symptoms included: (i) typical COVID-19 symptoms: temperature >100°F (37.8°C), cough, shortness of breath or respiratory rate >24/min and oxygen saturation <90%, (ii) atypical symptoms: chills without fever, malaise, behavioural change (including delirium, unusual apathy, aggressiveness or opposition to care), unusual rhinorrhea, nasal congestion, sore throat, myalgia, exhaustion, dizziness, headache, nausea, diarrhoea, falls, livedo, anorexia and hypothermia and (iii) residents’ characteristics including age, gender, length of stay at facility <90 or ≥90 days, as well as chronic comorbidities, including heart diseases requiring at least one medication, treated diabetes mellitus, history of stroke, kidney insufficiency (creatinine clearance <30 ml/min), haemodialysis, body mass index >25 kg/m² (overweight) or <18.5 kg/m² (malnutrition), moderate or severe cognitive decline according to the NH medical coordinator, use of antipsychotic drugs and smoking habits.

Nasopharyngeal testing for SARS-CoV-2 using rRT-PCR was performed in all residents as soon as a first resident was tested positive in the NH. Testing was repeated weekly in all previously negative residents until no new cases were identified for at least 14 days in the NH and in all positive residents until rRT-PCR became negative.

All residents underwent blood testing for SARS-CoV-2 nucleocapsid protein IgG using an enzyme-linked immunosorbent assay 6 to 8 weeks after the last resident was tested positive for SARS-CoV-2 in the NH [23].

**Statistical analysis**

Qualitative variables were described with frequency and proportions for each category. The description of quantitative variables was performed using mean and standard deviation and/or median, minimum and maximum values. Characteristics of positive or negative rRT-PCR residents were compared using Student’s or Wilcoxon–Mann–Whitney tests for quantitative variables according to the distribution, and Chi-2 or Fisher exact tests for qualitative variables. Symptoms that were distributed differently between positive and negative rRT-PCR residents (P < 0.20) were entered into a multivariate logistic regression analysis. A backward selection of variables was applied using the Akaike Information Criterion [24]. The significance of removing a variable from the logistic model was determined by the maximum likelihood ratio test. The goodness of fit of the models was assessed using the Hosmer and Lemeshow Chi-square test as well as the Area Under the receiver operating characteristic Curve (AUC) and its 95% confidence interval. An AUC equal to 0.5 suggests a non-discriminatory model; between 0.7 and 0.8 the discrimination is acceptable, and between 0.8 and 0.9 it is excellent [25]. The adjusted odds-ratios (OR) and their 95% confidence intervals were reported. No imputation method was used to handle missing data. The statistical significance threshold was set at 5%. Analyses were performed using SAS Enterprise Guide, v7.3 (SAS Institute Inc, Cary, NC, USA).

**Results**

**Characteristics of the NHs**

Among the 99 NHs of the area, 37 had at least one rRT-PCR-positive resident and 212 residents had positive rRT-PCR test results between 3 March and 10 June 2020. A total of 10 NHs reported at least 10 cases of rRT-PCR-positive residents but two had missing data. In the eight
Table 2. Reported symptoms in residents during the 14 days before testing

| Symptoms during the past 14 days | SARS-CoV-2 test results | P Value |
|---------------------------------|--------------------------|--------|
|                                 | Negative (N = 295)       |        |
|                                 | Positive (N = 161)       |        |
| Typical symptoms - no. (%)      |                          |        |
| At least one symptom            | 75 (25.4)                |        |
| At least two symptoms           | 29 (9.8)                 | <0.0001|
| At least three symptoms         | 9 (3.0)                  | <0.0001|
| Number of typical symptoms - mean (SD) | 0.41 (0.9) |        |
| Temperature > 100°F (37.8°C)    | 36 (12.2)                | <0.0001|
| Cough                           | 37 (12.5)                | <0.0001|
| Oxygen saturation < 90%         | 27 (9.1)                 | <0.0001|
| Respiratory rate over 24/min    | 8 (2.7)                  | <0.0001|
| Atypical symptoms - no. (%)     |                          |        |
| At least one symptom            | 102 (34.6)               | <0.0001|
| At least two symptoms           | 47 (15.9)                | <0.0001|
| At least three symptoms         | 12 (4.1)                 | <0.0001|
| Number of atypical symptoms     | 0.6 (0.9)                | <0.0001|
| Exhaustion                      | 33 (11.2)                | <0.0001|
| Falls                           | 23 (7.8)                 | <0.0001|
| Behavioural disorder            | 14 (4.7)                 | <0.0001|
| Anorexia                        | 4 (1.4)                  | <0.0001|
| Muscle pain                     | 1 (0.3)                  | <0.0001|
| Chills                          | 2 (0.7)                  | <0.0001|
| Sore throat                     | 0 (0.0)                  | 0.002  |
| Malaise                         | 1 (0.3)                  | 0.009  |
| Diarrhoea                       | 45 (15.2)                | 0.04   |
| Hypothermia                     | 18 (6.1)                 | 0.09   |

remaining NHs, all 456 residents were included in the analysis: 161 tested positive for SARS-CoV-2 (35.3%; range: 15.7 to 54.7%) and there was no drop out (Appendix 1).

Demographic characteristics of residents

Residents with a positive rRT-PCR test more often had cardiovascular or renal diseases, or a severe cognitive impairment. Pre-existing lung disease was not a risk factor for positive rRT-PCR testing (Table 1).

Symptoms during the 14 days prior to the testing

Typical symptoms were significantly more common in rRT-PCR-positive residents than in negative ones (on average, 1.9 typical symptoms vs 0.4 in negative residents, respectively, P < 0.0001). There were a significantly greater number of typical symptoms in rRT-PCR-positive residents (P < 0.0001). Temperature > 100°F (37.8°C), cough, oxygen saturation < 90% and respiratory rate > 24/min were all more prevalent in rRT-PCR-positive residents than in those who tested negative (P < 0.0001) (Table 2).

Atypical symptoms were also significantly more common in rRT-PCR-positive residents than in those who tested negative (on average, 1.9 typical symptoms vs 0.6, respectively, P < 0.0001). There were a significantly greater number of atypical symptoms in rRT-PCR-positive residents than in the negative ones (P < 0.0001). The most prevalent atypical symptoms observed in rRT-PCR-positive residents were exhaustion, falls, behavioural change, anorexia, muscle pain, chills, sore throat and malaise. Diarrhoea was more prevalent in rRT-PCR-positive residents but its prevalence was also high in residents who tested negative (Table 2, Appendix 2).

Symptoms of rRT-PCR-positive and negative residents are displayed in Appendix 3. Table 4 displays symptoms associated with a positive result for SARS-CoV-2 in the univariate and multivariate analyses. In the multivariate analysis, the symptoms associated with a positive rRT-PCR result were anorexia, exhaustion, falls/malaise, temperature > 37°C, oxygen saturation < 90% and behavioural change. The model AUC was 0.82.

Immunisation against SARS-CoV-2 in NH residents, depending on rRT-PCR test results

A positive rRT-PCR result predicted the development of SARS-CoV-2 IgG in 95.2% of cases [Positive Predictive Value IC95%: 93.1–97.3%]. A negative rRT-PCR result predicted the lack of immunisation against SARS-CoV-2 in 92.4% of cases [Negative Predictive value IC95%: 89.8–94.9%]. Among the 21 residents who repeatedly...
tested negative for SARS-CoV-2, those who developed antibodies against SARS-CoV-2 had more often a respiratory symptom and more often atypical symptoms, including especially diarrhoea, hypothermia, behavioural change and falls (Table 5). All asymptomatic rRT-PCR-positive residents developed antibodies against SARS-CoV-2.

**Death and hospitalisation rate**

A higher rate of hospitalisation and death was observed in residents with positive rRT-PCR testing (Appendix 1).

**Discussion**

The main results of this study are: (i) nasopharyngeal rRT-PCR testing has a high value in predicting immunisation against SARS-CoV-2; (ii) even when taking into account atypical symptoms, 17.4% of the PCR-positive residents are asymptomatic in the 14 days before testing; (iii) besides typical symptoms (fever, oxygen saturation <90%, but not cough), anorexia, behavioural change, exhaustion, malaise and falls in the 14 days before testing are independent predictors of a positive rRT-PCR test and (iv) 61.9% of residents who developed antibodies while having repeated negative rRT-PCR results had at least one typical or atypical symptom over the follow-up period.

Our study has several strengths. First, it was conducted in a large sample of NH residents who were tested across eight NHs facing a severe COVID-19 outbreak. Second, all residents were studied and there was no drop out during the study. Third, ascertainment of typical and atypical symptoms was almost complete since all studied NHs followed the regional Health Agency guidance published in March 2020. This guidance recommends to record systematically on residents’ files all unexplained symptoms—even those unusual for COVID-19—and to test residents for SARS-CoV-2 by rRT-PCR at the slightest doubt. Because atypical symptoms reported as COVID-19 symptoms in frail older persons are very common in NH residents, the assessment of typical and atypical symptoms in both resident tested positive and negative by rRT-PCR allowed us to determine whether typical and atypical symptoms are predictors of a positive testing for SARS-CoV-2 in NH residents. Fourth, the rRT-PCR positive or negative results were ascertained in all residents with no selection bias since the facility-wide testing was (i) implemented in all residents, even when asymptomatic, (ii) repeated in all negative residents until no new cases were diagnosed for at least 14 days and (iii) repeated in all positive residents until their test results became negative [5,6]. Fifth,
Table 5. Reported symptoms during the 14 days before rRT-PCR testing in residents tested negative for SARS-CoV-2: comparison of residents with positive vs those with negative SARS-CoV-2 immunisation

| Symptoms during the past 14 days | SARS-CoV-2 immunisation | P Value |
|---------------------------------|-------------------------|---------|
|                                 | Negative (N = 256)      | Positive (N = 21) |         |
| Typical symptoms - no. (%)      |                         |                     |
| At least one symptom            | 71 (27.7)               | 11 (52.4)          | 0.02    |
| Number of typical symptoms - mean (SD) | 0.38 (0.7)     | 0.95 (1.3)         | 0.01    |
| Shortness of breath             | 12 (4.7)                | 5 (23.8)           | <0.01   |
| Respiratory rate over 24/min    | 6 (2.3)                 | 3 (14.3)           | 0.02    |
| Atypical symptoms - no. (%)     |                         |                     |
| At least one symptom            | 96 (37.5)               | 14 (66.7)          | <0.01   |
| At least two symptoms           | 44 (17.2)               | 11 (52.4)          |         |
| At least three symptoms         | 16 (6.2)                | 7 (33.3)           |         |
| Number of atypical symptoms     | 0.64 (1.0)              | 1.9 (1.9)          | <0.01   |
| Exhaustion                      | 34 (13.3)               | 72 (28.6)          | 0.1     |
| Falls                           | 31 (12.1)               | 6 (28.6)           | 0.04    |
| Behavioural disorder            | 12 (4.7)                | 4 (19.0)           | 0.02    |
| Anorexia                        | 5 (1.9)                 | 2 (9.5)            | 0.09    |
| Chills                          | 0 (0.7)                 | 1 (4.8)            | 0.08    |
| Malaise                         | 0 (0.7)                 | 1 (4.8)            | 0.08    |
| Diarrhoea                       | 42 (16.4)               | 9 (42.9)           | <0.01   |
| Hypothermia                     | 11 (4.3)                | 5 (23.8)           | <0.01   |

IgG against SARS-CoV-2 were measured in all residents, and the period during which this study was conducted (March to June 2020, i.e. during the ‘first wave’ of the epidemic in our region) allowed us to ascertain a recent contact with SARS-CoV-2 in residents. rRT-PCR testing and immunisation against SARS-CoV-2 were performed in all residents, enabling the estimation of the negative predictive value of rRT-PCR testing in NH residents.

The present study does however have some limitations. First, doctors and nurses may have missed some symptoms that were not recorded in residents’ files. However, the high AUC value of our model (0.82) suggests that typical and atypical symptoms retained in the multivariate analysis predict a great part of rRT-PCR test results in the studied residents. On the contrary, it is possible that symptoms may have been overreported during that period of high anxiety in staff members. However, this bias does not affect the multivariate model since symptoms were probably overreported with the same magnitude in residents further tested positive and negative. Second, the study was conducted in NHs facing a COVID-19 outbreak. Therefore, whether our results can be extrapolated to COVID-19 residents from NHs less severely affected by the epidemic remains to be confirmed. In fact, the presence of a large number of cases in an NH can induce a high ‘viral load’ in the facility and a greater risk of repeated viral contacts that could modify residents’ symptoms and perhaps the development of antibodies.

The main difference between our results and those of previous ones is the proportion of asymptomatic rRT-PCR-positive residents, which was 56% (27 out of 48 residents) in Arons’ study [7] vs 17.4% (28 out 161) in ours. The difference is probably partly due to the atypical symptoms considered in our study (including exhaustion, falls, behavioural change, diarrhoea and anorexia) that have been shown to be possible COVID-19 symptoms in frail older subjects [8–21,26].

The results of the present study may have several possible implications.

The present study allows us to estimate the negative predictive value of rT-PCR testing, showing that 7.6% of the residents who repeatedly tested negative for SARS-CoV-2 developed antibodies against SARS-CoV-2. Among the 7.6% of residents with ‘false negative results’, a large part (61.9%) had at least one respiratory or atypical symptom that was not explained by another obvious cause in the 14 days before or after the first testing. This result suggests that SARS-CoV-2 infection prevention and control measures should be implemented in rRT-PCR-negative residents when they have typical or atypical symptoms consistent with COVID-19 (especially diarrhoea, hypothermia, behavioural change, malaise or falls) [27], even if it remains to be determined whether residents tested repeatedly negative but developing SARS-CoV-2 IgG may participate in virus transmission.

The percentage of NH residents tested positive for SARS-CoV-2 who developed SARS-CoV-2 IgG was very high (95.2%). All 28 asymptomatic rRT-PCR-positive residents developed SARS-CoV-2 IgG in the present study, suggesting the lack of ‘false-positive results’ in the residents of our sample. Because Arons et al. [7] showed that a major part of asymptomatic rRT-PCR-positive residents have a viable virus, the present result further confirms that the same infection prevention and control measures should be implemented in residents tested positive for SARS-CoV-2, whether symptomatic or not.

The excellent value of rRT-PCR to predict immunisation against SARS-CoV-2 strongly legitimates the strategy to diagnose COVID-19 in NH residents recommended in
the USA and in Europe that is based on rRT-PCR testing [5,6]. Most rRT-PCR-positive residents (95.2%) and 7.6% of rRT-PCR-negative residents developed SARS-CoV-2 IgG. It remains to be determined whether the development of antibodies against SARS-CoV-2 is long-lasting in immunised residents, therefore protecting them against a new infection, and whether the determination of the serologic status of residents may help to better prepare NHs to prevent a new COVID-19 outbreak.

Even if the number of asymptomatic rRT-PCR-positive residents is lower in the present study than in other studies, the presence of asymptomatic forms of COVID-19 in residents legitimates US and EuGMS guidance that recommends (i) testing all NH residents, even if asymptomatic, as soon as a new case of COVID-19 is diagnosed, (ii) repeating tests in all previously negative subjects once a week until the testing identifies no new COVID-19 cases for at least 14 days and (iii) performing appropriate infection and prevention measures [5,6].

The present study demonstrates that atypical symptoms have to be added to the list of symptoms that should be daily screened to identify the first SARS-CoV-2 residents as early as possible. Assessment of atypical symptoms adds to the prediction of COVID-19 infection in residents tested repeatedly negative by rRT-PCR (see above) and, above all, adds strongly to the prediction of a positive rRT-PCR testing in NH residents. Indeed, among symptoms already reported as being consistent with COVID-19 in frail older persons [8–20], anorexia, behavioural change, exhaustion, malaise and falls in the 14 days before testing were predictors of a positive rRT-PCR testing, and this independently of typical symptoms (fever, oxygen desaturation, but not cough) in our multivariate model. Since atypical symptoms can accompany infectious situations in general, the present results suggest that measures to prevent infectious diseases in NH residents, including influenza and pneumococcal vaccinations, should be implemented more than ever when SARS-CoV-2 circulates in the community. This could reduce the risk of confusion between symptoms linked to COVID-19 and to other infectious diseases, also because some patients with COVID-19 have had pneumonia [28].

The rate of death in infected residents was high (19.2%), but lower than in previous studies [3]. It remains to be determined whether the high hospitalisation rate (25.6%), aimed at reducing the workload of staff members [6], may have participated in this relatively low mortality rate.

Conclusions and implications

The present study strongly supports (i) a strategy based on rRT-PCR for an early identification of SARS-CoV-2 in NH residents, (ii) that NH residents with unusual fatigue, behavioural change, anorexia, malaise or falls should be tested by rRT-PCR for an early identification of the first SARS-CoV-2 cases, (iii) that facility-wide testing should include asymptomatic residents when a first SARS-CoV-2 case is identified, (iv) that rRT-PCR-negative residents with unexplained respiratory symptom, diarrhoea, hypothermia, behavioural change or falls should be managed, as a precaution, as SARS-CoV-2 residents, even if it remains to be determined whether they may participate in SARS-CoV-2 transmission and (v) that immunisation is quite systematic in residents tested positive for SARS-CoV-2. Whether immunisation may protect residents against a new SARS-CoV-2 infection remains to be elucidated.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

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