

Assessment of Post-COVID-19 Immune Response and Symptom Patterns Among Long-Term Care Facility Residents and Employees

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Abstract

Learning about the immune response and symptom patterns after the infection of SARS-CoV-2 is essential to protect populations at risk in the long-term care setting. The objective of this study was to assess post-infection immunity and record symptoms patterns in residents and staff in nursing home. A prospective cohort design was used to track serological markers, reinfection, and the presence and duration of symptoms among the participants in a six months follow-up. Early results show that although the majority of the people encountered detectable antibodies, the severity and period of symptoms were diffused among residents and staff. It is worth noting that the fatigue and respiratory complaints were found to be long lasting in the older residents as opposed to their younger staff members. These outcomes highlight the role of individualized post-infection surveillance and preventive measures in high-risk congregate environments as a guide in vaccination and infection control policies.

Keywords: Post-COVID-19 immunity, nursing home residents, long-term care staff, SARS-CoV-2, symptom monitoring, serological response, reinfection risk, cohort study.

1.Introduction

The development of SARS-CoV-2 at the end of 2019 is a radical shift in the world healthcare, and the ensuing COVID-19 pandemic revealed a significant weak point of healthcare systems globally. One of the most at risk groups was the elderly living in long-term care facilities, as the combination of old age, numerous comorbidities, and a high concentration within the population formed an ideal storm of viral transmission and disastrous results. The unequal distribution of the pandemic struck nursing homes at the beginning of its spread and the facilities constituted an astounding proportion of COVID-19 fatalities despite the fact that they only had a fraction of the population.



FIGURE 1 Analyzing COVID-19 Impact on Nursing Homes

An example of such a disastrous trend is Belgium, in which the proportion of citizens aged 65 and above in nursing homes amounts to about 10 per cent(1). During the period between March and June 2020, over 60 percent of all COVID-19 fatalities in Belgium were among nursing home residents, which illustrates the urgent needs of this patient group. This terrible toll was not only the biological vulnerability of the elderly to severe outcomes caused by COVID-19 but also a manifestation of the difficulties in organizing effective methods of infection control in residential care facilities where socialization and active care are the main components of the quality of life and overall operation.

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The heightened susceptibility of elderly populations to COVID-19 stems from multiple interconnected factors. The age-associated deterioration of the immune system, immunosenescence, undermines the primary response of an immune system to infections and the formation of a protective immune system after recovery. This biological fact overlaps with the fact that the prevalence of chronic conditions in nursing home residents is very high, and these diseases include cardiovascular disease, diabetes, chronic respiratory illnesses, and cognitive impairment. Such comorbidities not only predispose to the risk of having severe COVID-19 but also may complicate the clinical identification of infection as symptoms may be atypical or may be related to underlying conditions.

The clinical manifestation of infection with SARS-CoV-2 differs significantly in relation to age, and with the emergence of new information, it may be important that older people may have a different symptomology than younger patients. Research shows that in the elderly patients a greater number of infections have no symptoms, which may help to facilitate the transmission without its detection in the care facilities. Older adults might also display symptoms in an atypical manner and they might not have the typical symptoms of COVID-19 such as the presence of a fever and respiratory symptoms. Rather, older adults can manifest with confusion, falls, or the general deterioration, and, thus, it can be difficult to diagnose them early and isolate them(2).

What adds to these clinical dilemmas are the complicated epidemiological dynamics in nursing homes with both residents and staff playing a role in the transmission dynamics. The occupational hazards associated with work in such environments are distinctive, as healthcare workers are often in close contact with possible cases of infection, but the occupational challenges of adherence to high standards of infection control in the course of regular care are practical. Bi-directional risk of infection between the staff and the residents presents complex chains of infection that can quickly disseminate to the whole facility.

The presence of another pathogen that interacts with the SARS-CoV-2 to complicate infection control in nursing home further enhances the complexity of infection control. Seasonal influenza, respiratory syncytial virus, and other respiratory viruses co-exist with SARS-CoV-2, and may be co-infected, as well as may be diagnosed with them. SARS-CoV-2 co-infection has been reported to be significant with many respiratory pathogens including seasonal coronaviruses, influenza viruses, rhinoviruses, and human metapneumovirus. Although there has been an initial indication that co-infection with influenza A can increase the viral loads and infectivity of SARS-CoV-2, the larger consequences of such interactions are not well understood.

The interpretation of the association between previous infection with SARS-CoV-2 and the susceptibility to respiratory illness has urgent implications to the nursing home management and public health policy. As soon as the past infection offers protection against the new one or the severity of the following respiratory diseases, this information would inform the measures of cohorting residents, staff scheduling, and resources distribution. On the other hand, in that case where prior infection offers no protection or even induces susceptibility to other pathogens, alternative methods of infection prevention and control would be justified.

Protective responses to infection by SARS-CoV-2 do not seem to develop in all age groups equally, with older people showing more heterogeneous and possibly less durable immune responses. This difference in age response to the immune system also applies to vaccination reactions, where the elderly tend to produce less antibodies and provide less protection than the younger adult. This is essential in understanding the differences to formulate an evidence-based practice in defending vulnerable populations in congregate care settings.

The nursing home setting poses special difficulties in the analysis of the dynamics of infectious diseases. Closure of communities, coupled with extensive record keeping of resident health conditions and frequent staff interaction, offers a chance to study patterns of infections more accurately than can be done in community environments. Nevertheless, such a population also requires thorough ethical deliberations and effective adjustments of research procedures due to the vulnerability of this population.

2.Methods

2.1 Study Design and Theoretical Framework

The PICOV study was based on the prospective multi-centre cohort design to investigate the association between previous SARS-CoV-2 infection and the risk of respiratory disease. This longitudinal design was chosen to generate the temporal dependencies between exposure history and future health outcomes and control the confounding variables with the help of a thorough characterization of participants. The research design was based on the concepts of infectious disease epidemiology, i.e., analyzing the effect of prior exposure to the pathogen on host susceptibility to other related and non-related respiratory pathogens(3).

The theoretical mechanisms behind this research are based on the already known concepts of immunology such as cross-reactive immunity, trained immunity and development of immune memories. Past studies on the interactions of respiratory viruses formed the basis of hypothesizing that SARS-CoV-2 infection may have counterintuitive effects on subsequent responses to other respiratory infections, due to either protective cross-reactivity or immune system regulation that may either prime or weaken future infections.

2.2 Facility Selection and Recruitment Strategy

The nursing homes in all three regions of Belgium (Flanders, Wallonia, and Brussels) were recruited based on geographic representativeness as well as to represent regional differences in care practices, demographics within the population, and epidemic trends. A systematic approach was initially used to contact more than 200 facilities with the help of healthcare networks, professional associations, and direct contact with administrators of these facilities.

Facilities that had proper infrastructure to collect and store biological samples, had a developed electronic health record system, and administrative capacity to facilitate research activities were given preference. Facilities were required to show consistent staffing trends and low turnover rates were expected so as to reduce loss to follow-ups within the study period. Also, the nursing homes were to have had at least some cases of COVID-19 during the March-August 2020 to guarantee a sufficient number of both previously infected and naïve individuals.

Out of the facilities contacted, 26 nursing homes decided to take part, which is about 13 percent of the contacted facilities. This engagement percentage displayed the high operational pressure that nursing homes had to face during the pandemic since most of them had limited resources or capacity to conduct research activities when dealing with the current problems of infection control(4).

2.3 Participant Classification and Exposure Definition

The participants were categorized as two major exposure groups with objective evidence of being previously infected with SARS-CoV-2. The previously infected group comprised those individuals with a positive RT-qPCR test between March and August 2020 and/or with baseline (i.e., SARS-CoV-2 antibody), detected SARS-CoV-2 antibodies. The naïve group included those whose antibodies were not detected at the baseline and who had a negative RT-qPCR result in the defined time frame.

Such a method of classification took note of the drawbacks of using historical RT-qPCR findings only, which could have excluded asymptomatic infections or persons not tested in the first pandemic wave. Base serological testing gave a deeper profile of past infection status, including those who might have had undiagnosed infection.

A focused serological screening protocol was used to overcome the problem of identifying the participants who were previously infected in the facilities that had limited or no history in testing. In nursing homes with less than one-half of residents and staff with positive RT-qPCR results patient and staff history the rapid diagnostic tests were used to identify individuals previously infected who could have otherwise been classified as naïve(5).

2.4 Framework of Sampling and Biological Specimen Collection

The biological sampling procedure was tailored so as to sample both of the baseline immune status and dynamic alterations over the course of the study. At the time of enrollment, baseline sampling was done which consisted of nasopharyngeal swabs to detect active infection, serum to detect the presence of antibodies, heparinized blood to isolate peripheral blood mononuclear cells, and saliva to test mucosal immunity.

The sampling was time-based and was event driven. Those who acquired influenza-like illness or developed symptoms of acute respiratory infection within five days of onset had immediate specimen collecting with a time span of five days and convalescent sampling of two to three weeks. With this paired sampling method, it was possible to evaluate immune response to new infections and establish the causative agents.

Further sampling was done after administering seasonal influenza vaccination and the samples were taken two weeks after vaccination to determine immune responses. Sampling at the end of the study was planned to be done in spring 2021 to determine the change in the immune markers throughout the total period of follow-up.

Processing of specimens was performed in line with standard protocols to provide quality and uniformity of samples collected in different locations. The nasopharyngeal swabs were preserved in viral transport medium at the right temperatures and transported to central laboratories within a period of 24-48 hours. Isolates were done with the standardized centrifugation protocols on serum samples, and peripheral blood monocytes were isolated through the density gradient centrifugation within a period of 24 hours after collection.

2.5 Questionnaire Design and Data Collection Instruments

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To ensure that all details of the participants were obtained, data collection framework included both general and study-specific questionnaires. Baseline questionnaires gathered demographic, medical history, and medication use, functional status, and specific data on any prior COVID-19 episode that occurred in March-August 2020.

Symptom measurement involved use of structured recall questionnaires that aimed at reducing bias on reporting and at the same time providing clinically important data. The participants were requested to describe certain symptoms, the duration of the symptoms, their severity, and their effect on daily activities in any previous COVID-19 episode. The symptom inventory comprised common manifestations of COVID-19 (fever, cough, dyspnea, fatigue) and less frequent manifestations that could be more prevalent in older groups of patients (confusion, falls, anorexia).

Standardized measures were also introduced to measure overall health status as well as functional capacity. The Clinical Frailty Scale was used to measure frailty in residents and the EQ-5D-5L was used to measure a validated health-related quality of life. Residents were also assessed based on the Katz Activities of Daily Living scale which assessed functional independence and through the Mini-Mental status examination which assessed cognitive status(6).

Occupational exposure assessment of staff participants involved detailed information regarding job assignments, workplace locations in facilities, personal protective equipment use, and the worker being assigned to a special COVID-19 care unit. This data played a significant role in the knowledge about the existence of heterogeneous exposure risks among staff categories.

2.6 Laboratory Methods and Analytical Approaches

SARS-CoV-2 nasopharyngeal swab testing was based on RT-qPCR of E gene subsequently, using standard protocols with the cycle threshold to determine positivity of 40. The methodology offered sensitive detection of on-going infections but specific to SARS-CoV-2.

Serology testing was by the Wantai SARS-CoV-2 Ab ELISA that identifies antibodies against the receptor binding domain with a high specificity (99.6%), and sensitivity (100% at 14 days post-symptom onset). The assay identifies IgG, IgA, and IgM antibodies at the same time, giving the overall evaluation of humoral immune response.

Quality control factors comprised frequent equipment calibration, positive and negative controls, and through the external quality assurance schemes. The inter-laboratory comparisons were performed to balance consistent results at every site of testing.

2.7 Statistical Analysis Plan

The methodology involved the descriptive and inferential statistics to characterize the study population and to test the basic hypotheses. Appropriate measures of central tendency and dispersion were used to summarize the baseline characteristics of the continuous variables and proportions used to summarize the categorical variables. Shapiro-Wilk test and visual analysis of quantile-quantile plots were used to test the assumptions of normality. Bivariate comparisons were done using chi-square tests when dealing with categorical variables and t-tests or Mann-Whitney tests when dealing with continuous variables, respectively, according to distributional assumptions.

The main analysis was aimed at contrasting the patterns of symptoms in naive and previously infected participants, stratified by the resident/staff status. Secondary analyses were conducted evaluating the factors related to asymptomatic infection and baseline persistent symptoms.

Patterns of missing data were considered and ways of dealing with the missing data was effected depending on the mechanism of missingness and what type of analysis was being done.

3.Results

3.1 Study Population Characteristics and Enrollment Outcomes

The recruitment process started on September 24th, 2020 and ended on December 8th, 2020 with 1,375 persons having informed consent and providing it in the 26 nursing homes participating in the program. The cohort that received the last analysis included 1,226 subjects excluding 116 who dropped out of the study (8.4% attrition rate). Most common causes of withdrawal were reported to be study burden (n=33), failure to complete baseline measures, and logistical reasons that involved continued management of the pandemic in facilities.

Demographic distribution in the study population showed the projected demographic ratios in a nursing home environment with residents aged 81.9 (mean) years (10.7) as opposed to staff at 44.2 (mean) years (11.5). The two groups were dominated by female participants, who represented 64.2 and 85.3 percent of residents and staff

participants respectively. The large proximate majority of respondents (91.2 percent) were European ethnicity (demographic composition of Belgian nursing homes).

The typical patterns of institutional care settings were found in baseline health characteristics. The average BMI of the residents was 25.5 kg/m² (± 5.3) with the majority of the participants (72.2) not having smoked in the past. Employees were equal in BMI (26.1 ± 4.8 kg/m²) and smoking status (72.7% non-smokers). Physical activity indicators were also significantly different between groups with 46.9% of staff indicating that they spent at least 60 minutes of daily activity versus only 13.0% of residents(7).

3.2 SARS-CoV-2 Exposure History and Serological Classification

Testing data in the previous years indicated that 97.6% of them (n=1,197) have had an RT-qPCR testing between March and August 2020, with a smaller proportion (16.3, n=200) having serological testing in the same period. On entry into the study, 18 participants (1.5% endorsed, by RT-qPCR, active SARS-CoV-2 infection.

The combination of the historical testing data with the baseline serological results facilitated an overall classification of exposures. Depending on the baseline and/or positive RT-qPCR findings observed in March-August 2020, 640 participants (52.2) were pre-infected and 586 participants (47.8) were infection-naïve.

Examination of the sample of already-infected subjects showed that there are differences in the distributions of immune markers and testing history. Of the 640 historical RT-qPCR-positive participants (n=640), 397 (62.0) had positive history and positive baseline antibody, 182 (28.4) had positive history and negative baseline antibody, and 61 (9.5) had positive history and positive baseline antibody.

Importantly, the ratio of naïve to previously infected individuals was no different between residents and staff (52.4% vs 47.4% naïve, respectively; $p=0.52$) which suggests that the balanced objectives of the study were achieved.

3.3 Age-Stratified Differences in Infection Patterns

The correlation age-infection characteristics showed that there were substantial distinctions in residents and staff populations. Among the participants who had a history of infection, residents exhibited the best rates of serologically-confirmed asymptomatic infection relative to staff members (20.5% vs 12.4%, $p<0.0001$). This trend indicates that older adults might have undergone undetected infections more frequently the possibility being because of unusual, or lack of symptom manifestation.

On the other hand, employees registered more prevalence of documented symptomatic infection with positive RT-qPCR results. The 35.5% of previously infected staff had both positive RT-qPCR and detectable antibodies at baseline versus 24.4% of residents ($p=0.0004$). This disparity is probably due to the increased testing in symptomatic disease and more characteristic manifestation of the symptoms in younger adults.

Isolated seropositivity (antibodies present without observed positive RT-qPCR) as a pattern was more prevalent in residents (24.4% versus 14.2% in staff, $p=0.0004$) again supporting the hypothesis that the elderly population had more prevalent asymptomatic or unrecognized infections.

3.4 Symptom Profile Analysis During Initial Infection Period

Retrospective symptom assessment showed that there were significant differences in the number of symptoms reported by naïve and previously infected participants, with the previously infected participants reporting a much higher number of symptoms in March-August 2020 (5.5 ± 3.9 vs 3.0 ± 2.3 symptoms, $p<0.0001$). This disparity was most evident among the staff members where the previously infected reported 6.1 ± 4.0 symptoms against 3.1, 2.2 symptoms in naïve members of staff ($p<0.0001$).

The symptom difference between residents was smaller but statistically significant with previously infected residents reporting 3.1 symptoms compared to 1.9 symptoms in naïve residents ($p=0.0155$). This differences of smaller extent can be associated both with the larger percent of asymptomatic infections among the elderly population and the possible recall bias in this population.

There was significant variation in symptom spectrum between residents and staff among those who were confirmed to have had previous infections. The manifestations of classical COVID-19 symptoms were observed in staff members, and fatigue (56.6%), anosmia/ageusia (44.7%), and headache (43.1) were the most frequent ones. By comparison, fatigue (21.3%), fever (20.7%), and mentions in infected residents were significantly lower than anosmia/ageusia (6.4%), and headache (3.7%).

3.5 Comparative Symptom Burden Between Age Groups

The difference in the reporting of symptoms between the age groups went across several symptom categories. Cough and dyspnea were reported in 33.0 and 32.7% of the infected staff and 18.1 and 16.0% of the infected

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residents, respectively. A similar pattern was observed in gastrointestinal symptoms, neurological symptoms, and pain syndromes, as well as, higher prevalence in staff(8).

In previously infected individuals, residents (59.0% (n=111) out of previously infected reported no symptoms during their infection, versus 28.1% of staff members (n=127)). This observation is consistent with the rising literature that indicates a greater number of cases of asymptomatic COVID-19 in the aged populations, but it is also possible that recall bias could also play a role in this discrepancy.

This was especially contrasting on the symptoms of the senses, with a loss of taste or smell being reported in less than 7% of the infected residents, versus almost 45% of the infected staff. This disparity could be due to age-related changes in the baselines of sensory activity that may conceal the infection-induced changes or could represent the real disparity in the viral tropism of the age groups.

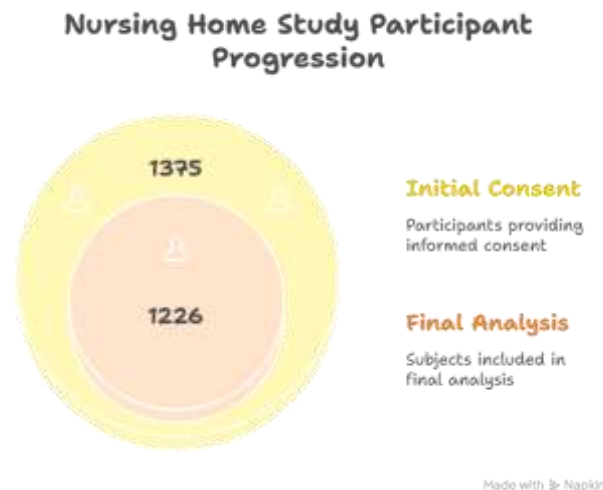


FIGURE 2 Nursing Home Study Participant Progression

3.6 Persistent Symptom Assessment at Baseline

Persistent symptom assessment at baseline sampling (1-10 months post-infection) demonstrated that there are still the health effects with the predominance of the members of staff. Among the 640 people who had been infected previously, 94 (14.7%) affected by the persistent symptoms at the baseline and staff members were disproportionately affected (86 staff vs 8 residents with persistent symptoms)(9).

Fatigue was the most common among staff patients with persistent symptoms (55.8%), then persistent anosmia/ageusia (39.5%), and dyspnea (36.0%). The low prevalence of residents who reported persistent symptoms (n=8) restricts the ability to analyze the data in detail, but cough (50.0%) and fatigue (25.0) had the highest prevalence of ongoing problems.

The low prevalence of persistent symptoms in residents (4.3% of residents who had been previously infected) compares unfavourably to the prevalence among staff (19.2% of staff who had been previously infected), indicating either improved recovery in the elderly or a possibility of under-reporting of persistent symptoms in the elderly.

3.7 Baseline Health Status and Functional Assessment

The various population models of the institutional care were demonstrated by the baseline health assessment of residents. The Clinical Frailty Scale test revealed that frailty levels were variable with Katz Activities of Daily Living scores reflecting that the care requirements were high, as is the case with nursing home patients. Mini-Mental State Examination scores reflected a cognitive functioning that was in agreement with the inclusion criteria of the study although a detailed cognitive data is yet to be analysed.

Occupational characteristics of the staff members indicated the heterogeneous nature of the nursing home workforce with nurses assistants (29.7) and nurses registered nurses (23.2) being the largest professional groups. Administrative (10.2), support (11.4) personnel were also large proportions of the workforce, with 6.1 percent of the workforce represented by specialized COVID-19 units during the study period.

Professional role allocation among staff participants offers valuable context on the assessment of exposure risk since job categories are likely to have a different degree of patient contact and infection control issues at the time of the pandemic.

4. Conclusion

Findings of the PICOV study baseline indicate that there are significant differences in the age-associated patterns of SARS-coV-2 infection and the symptom manifestation in nursing home settings. Such variations have direct consequences on the strategy of infection control, clinical management, and subsequent research in vulnerable populations.

Age-Related Disparities in COVID-19 Manifestation

The most striking finding concerns the substantial differences in symptom burden between elderly residents and younger staff members. Past-infected nursing home patients had an average of 3.1 symptoms in comparison to 6.1 among the staff, or a clinically significant difference that does not rely on statistical significance. Such a difference hints that the old screening methods based on symptoms may not possess the ability to detect infections among older populations, in which the presence of asymptomatic or minimal symptomatic manifestations is more common.

The percentage of infection among residents is higher (20.5) than that of staff (12.4), which defies the traditional beliefs about COVID-19 manifestation and has a direct reflection on infection control policies. The results indicate that nursing facilities might have to depend more on regular surveillance tests instead of symptom testing to detect infected patients. The fact that a large proportion of infections in residents with confirmed infections demonstrated atypical or minimal symptoms suggests that fever and respiratory symptom screening protocols though helpful, might fail to detect a significant proportion of infections in this population.

Implications for Clinical Management and Infection Control

The age-based stratified symptom patterns that have been reported in this study offer evidence-based factors that can be used to customize clinical assessment models to various populations in nursing homes. Most of the infected residents had fatigue and fever, an unusual pattern in the classical constellation of COVID-19 symptoms manifested in staff, which implies that the use of a uniform set of clinical evaluation protocols should not be used universally among different populations.

The observation that almost 60 percent of infected residents in the past indicate that they had no symptoms in the course of their infection, as compared to only 28 percent of the staff, has significant repercussions on the procedure of contact tracing and quarantine. These data indicate that chains of transmission in nursing homes can be more complicated than it was previously thought, and a significant role belongs to asymptomatic or minimally symptomatic residents, who could not be detected through conventional screening strategies.

The baseline sampling of the differential rates of persistent symptoms (residents 4.3-staff 19.2) deserves attention. Although this may indicate improved recovery in the ageing groups, it may also indicate under-reporting of persistent symptoms in cognitive impairment or communication challenged residents. Clinicians ought to be more keen on the nuanced indicators of lingering symptoms amongst elderly populations because of the possibility of attribution bias where new symptoms could be misdiagnosed as sequelae of existing conditions instead of post-COVID.

Future Research Directions and Clinical Applications

The results of the baseline are used to set up a basis of the further follow-up of the study whose results will be solid data on whether previous SARS-CoV-2 infection affects the vulnerability to the occurrence of the subsequent respiratory infections. Differences in the patterns of symptoms and serological reactions observed in the age groups imply that protective immunity might also vary, and this could have the consequences in terms of vaccination policy and the prevention of infections.

The relationship between baseline levels of antibodies, the severity of symptoms in the first infection, and the risk of secondary infection should be analyzed in the future. This observation that 9.5 percent of the former infected individuals had unmeasurable antibodies at baseline, deserves careful research on factors linked to antibody decline and its impact on the risk of reinfection.

Age-specific clinical assessment instruments and infection control measures are to be developed based on the patterns of symptoms of differentials recorded in this study. The healthcare systems might be required to come up

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with different screening algorithms between the elderly and the younger populations, where more priority should be done on routine surveillance tests among the vulnerable elderly populations.

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Conflicts of interest

The authors have no conflicts of interest to declare

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