ORCHESTRA

Connecting European Cohorts
to Increase Common
and Effective Response to
SARS- CoV-2 Pandemic

DELIVERABLE TEMPLATE

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Report on serology analysis of retrospective COVID-19 cohorts

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Project Management Guidelines

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Executive summary

WP and deliverable context

The present report is part of ORCHESTRA project, a three-year international research project aimed at tackling the coronavirus pandemic. ORCHESTRA provides an innovative approach to learn from the pandemic SARS-CoV-2 crisis, derive recommendations to further management of COVID-19 and be prepared for the possible future pandemic waves. The ORCHESTRA project aims at delivering sound scientific evidence for the prevention and treatment of the infections caused by SARS-CoV-2 assessing epidemiological, clinical, microbiological, and genotypic aspects of population, environment and socio-economic features. The project builds upon existing, and new largescale population cohorts in Europe (France, Germany, Spain, Italy, Belgium, Romania, Netherlands, Luxemburg, and Slovakia) and non-European countries (India, Perú, Ecuador, Colombia, Venezuela, Argentina, Brazil, Congo and Gabon) including SARS-CoV-2 infected and non-infected individuals of all ages and conditions. The primary aim of ORCHESTRA is the creation of a new pan-European cohort applying homogenous protocols for data collection, data sharing, sampling, and follow-up, which can rapidly advance the knowledge on the control and management of the COVID-19. Within ORCHESTRA project, the Work Package 6 (WP6) aims at providing innovative laboratory capabilities combining serology, immunology, viral and human genomes, microbiota and epigenetic analysis. It aims describing markers and physiopathology of various COVID-19 outcomes including severe cases, long COVID and vaccine efficiency across various patients' populations gathered within ORCHESTRA cohorts.

The objectives of the WP6 are distributed in two parts: (1) a retrospective part on frozen samples obtained during 2020 and (2) a prospective part starting in 2021. The goal for the serological markers part is to allow the description of the SARS-CoV-2 variants (both known variants and novel mutations) according to epidemics waves, stages of SARS-CoV-2 infection (mild vs severe), setting (outpatients vs hospitalized), and outcome (survivors vs non-survivors).

Content of the document

The present report describes the number of tested serological points and serological markers performed in the context of the retrospective study. The objective is to allow the description of serological markers across patients included in the retrospective part of the Orchestra study to allow its analysis along with viral variant, genomic, microbiota data and clinical data for all included patients with such available data.

In this report we provide the number of samples tested for all evaluated serological markers.

Dissemination level: Public

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Core content

Rational

The kinetics of the immune response, its magnitude, and its relationship to disease severity during SARS-CoV-2 infection have been quite extensively documented. Several works suggested that higher titers of anti-S1 and anti-N IgG and IgM positively correlate with age and the level of lactate dehydrogenase [1]. Notably, asymptomatic COVID-19 patients have a weaker immune response and faster and greater reduction of IgG titer [2], whereas several longitudinal studies have demonstrated that neutralizing antibody responses are more robust and are associated with severe clinical manifestations [3–6]. However, Ab titers may vary greatly in different patients, independently of the clinical course of SARS-CoV-2 infection, and up to 20% patients may have undetectable antibody titers only 3 weeks after a confirmed infection [2,7].

On the other hand, more than two years after the SARS-CoV-2 emergence, the diagnostic of COVID-19 relies on several assays detecting either SARS-CoV-2 antigens or its RNA in a various range of samples. The gold standard remains to date the use of reverse-transcriptase polymerase chain reaction (RT-PCR) performed on nasopharyngeal (NP) swabs [8]. Other techniques can be applied either molecular assays, such as loop mediated isothermal amplification (LAMP), or non-molecular, such as chemiluminescent immunoassays (CLIA) or lateral flow rapid antigen tests. Those methods often present a lower sensitivity, especially for cycle thresholds (Ct) values above 33 [9,10]. Other matrices such as saliva, respiratory aspirates or bronchoalveolar lavages can also been used and provide useful information. Non-respiratory matrices such as plasma or feces, have also been evaluated for RT-PCR detection [11–13].
RT-PCR techniques, nevertheless being the most sensitive methods, also provide an estimation of the viral load by providing a Ct value. Several works have demonstrated a link between the nasopharyngeal viral load and the disease severity [14]. This link is also questioned by other studies [15], and, indeed, nasopharyngeal Ct values present several pitfalls blurring the quality of quantitative assessment. Thus, the Ct values for a specimen vary between assays due to sample collection, extraction conditions, targeted genes, primers or threshold fluorescence values [16,17]. Outside Ct variations, NP samples can also be negative despite an ongoing COVID-19 at the earlier stage of the disease or, on the contrary, at the latter stage of the disease [18].
Blood samples have also been used for direct SARS-CoV-2 detection by RT-PCR assays. If the sensitivity is lower than respiratory samples, it seems associated with disease severity even if some discrepancies exist regarding this association [12,13]. Outside genomic detection, several works have also evaluated the detection of N-antigen in blood. This detection of a free-antigen in patients' serum, a first in a viral respiratory disease, appears to provide a good sensitivity for clinical diagnosis [19,20], could also be detected despite negative NP RT-PCR, suggesting it also reflects the viral replication in the lung and not only the NP area [19]. Moreover, very recent works suggested an association of N-antigen sera levels with disease severity that need to be confirmed on larger cohort and more deeply analyzed [21–23].

Thus, N-antigen detection and levels assessment could provide a cheap, easy-to-use, useful diagnostic tools and provide a better prognostic assessment than NP viral loads. However, the kinetic of this new serum marker, along with the kinetic of circulating anti-SARS-CoV-2 antibodies, has not been deeply evaluated. In this work, we used sequential samples from hospitalized patients presenting various degrees of disease severity to assess and model the N-antigen dynamic, the levels of anti-N, anti-S and anti-RBD antibodies and their association to disease severity.

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Description of the conducted tests

All sera samples were collected at Inserm (Laboratoire de Virologie, Hôpital Bichat Claude Bernard) for FrenchCOVID cohort, at the University Medical Center Groningen for the COVID Home cohort (UCMG) and at Department of Medical and Surgical Sciences, University of Bologna (UNIBO). Several serological markers were performed:

- **N antigenemia quantification using COV-Quanto® assay (AAZ, France)**
  N=1172 sera samples

- **IgG anti-N, anti-S and anti-RBD quantification using V-PlexTM panel assay (Meso Scale Discovery, USA)**
  N=1172 sera samples for all three markers

- **Fully automated serological methods (IgG II Quant anti-SARS-CoV-2 assay, Alinity, Abbott; SARS-CoV-2 S1/S2 IgG, Liaison XL, Diasorin)**
  N=173 sera samples

All corresponding results have been provided to the WP6 microbiological database and included in the analysis for corresponding markers (N-antigen, anti-N, anti-S and anti-RBD kinetics evaluation).

Description of planned additional assays

Sera samples are being shared with other Orchestra WP6 partners to allow evaluation of additional innovative serological markers.

- **Anti-IFN IgG detection using in-house assay**
  Inserm, Institut Imagine, Paris, France (Pr Laurent Abel)
  Progression: samples to be send on November 2021, results planned for S1 2022.

Description of the modelling approach

We reconstructed the N-antigen kinetics by considering this biomarker as a plasmatic proxy for the nasopharyngeal viral load. In this sense, we used a target-cell limited model of viral replication described previously for the modelling of nasopharyngeal viral load [14,24,25], to which we added a transfer rate to the plasmatic/extracellular compartment. This model includes 3 types of cell populations: target cells (T), infected cells in an eclipse phase (I1) and productively infected cells (I2). Target cells T are infected at a rate β; once infected, cells become productive after a latency period with mean duration 1/k (d). Productive infected cells are then naturally lost with a constant rate δ (d^{-1}). Viral particles are produced at a rate p (virions/cell/day), among which only a proportion µ is infectious. The infectious viral particles are noted Vi and the non-infectious particles are noted Vni. The viral particles are then transferred to the plasmatic compartment at a constant rate R and cleared at a rate E1. This rate R takes into account both the proportion of viral particle that become antigenic particles and the pace at which it is transferred to the bloodstream. We also modeled the increase in the elimination of the N-Antigen due to the development of the immune response in the plasmatic compartment. For that purpose, we used a phenomenological model to reproduce the increase of anti-

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N IgG over time, and we assumed a non-linear relationship between and the clearance rate of N-Antigen, where E_{max} represents the maximal clearance rate of infected cells due to IgG response and IgG_{50} represents the antibody concentration required to achieve half of this effect. The model is given by the following equations:

$$\frac{dT}{dt} = -\beta V_i T$$

$$\frac{dI_1}{dt} = \beta V_i T - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

$$\frac{dV_i}{dt} = p\ \mu\ I_2 - cV_i$$

$$\frac{dV_{ni}}{dt} = p\,(1-\mu)\ I_2 - cV_{ni}$$

$$\frac{dAg}{dt} = R\,(V_i + V_{ni}) - E_1 Ag\ - E_{max}\ \frac{IgG(t)}{IgG(t)+IgG_{50}} Ag$$

Results and comments

The results obtained are depicted in the file joined to this deliverable.

Briefly, we included 1345 samples throughout the included cohorts for those serological markers analysis. Among the corresponding patients, 66% were male and they presented a median age at 63 years [IQR: 52-71]. A total of 82, 96 and 142 patients were included in the Death, ICU and Hospital groups for the N-antigen prognostic marker analysis, respectively. The Death group presented higher proportions of male patient, >65 years old patients and higher levels of antigenemia at the first available time point. The delays between symptoms onset and hospitalization were similar across groups (cf. Table 1).

Variable	Overall (n=320)	Hospital group (n=142)	ICU group (n=96)	Death group (n=82)
Male gender	236 (66.1%)	79 (55.6%)	67 (69.7%)	69 (81.4%)
Age ≥ 65 years old	162 (45.4%)	45 (31.6%)	38 (39.5%)	46 (56.1%)
Hypertension	134 (42.9%)	43 (30.2%)	40 (41.6%)	35 (42.6%)
Chronic cardiac disease	68 (20.9%)	23 (16.1%)	15 (15.6%)	20 (24.3%)
Chronic pulmonary disease	46 (13.8%)	15 (10.5%)	13 (13.5%)	14 (17.1%)
Asthma	33 (10.2%)	16 (11.2%)	10 (10.4%)	7 (8.5%)
Chronic renal disease	33 (9.9%)	11 (7.7%)	6 (6.2%)	13 (15.8%)
Delay between SO[a] and hospitalization *median [IQR]*	8 [5-10]	8 [6-11]	7 [5-10]	7 [4-10]
First N antigenemia[b] *log_{10} pg/mL – median [IQR]*	2.2 [1.60-3.27]	1.9 [0.80-2.43]	2.4 [1.68-3.43]	3.3[2.09-3.97]

a: Symptom Onset
b: within the first 5 days of hospitalization

Table 1. Patients' main characteristics according to their groups.

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The sensitivity of N-antigenemia was 79% (131/165) within the first 10 days SSO (since symptoms onset) and 62% (365/589) from 11 to 30 days SSO. Positivity rates were significantly different across severity groups from 0 to 15 days SSO: 95% (95/100), 64% (118/183), 79% (83/105) ($p<0.001$) for Death, ICU and Hospital groups, respectively. Among positive patients, a significant gradient was found in the levels of N-antigenemia according to disease severity, with median levels of 302, 134 and 89 in Death, ICU and hospital groups, respectively. Similar relationships were found when stratifying on the time SSO (see figure). Overall, 95, 80, 43 and 22% of N-antigenemia >10,000, >5,000, >1,000 and <1,000 pg/mL corresponded to patients who died. IgG antibodies titers were not correlated to severity and the presence of both sera N-antigen and anti-N IgG was observed for 42% (490/1166) samples (Figure 1).

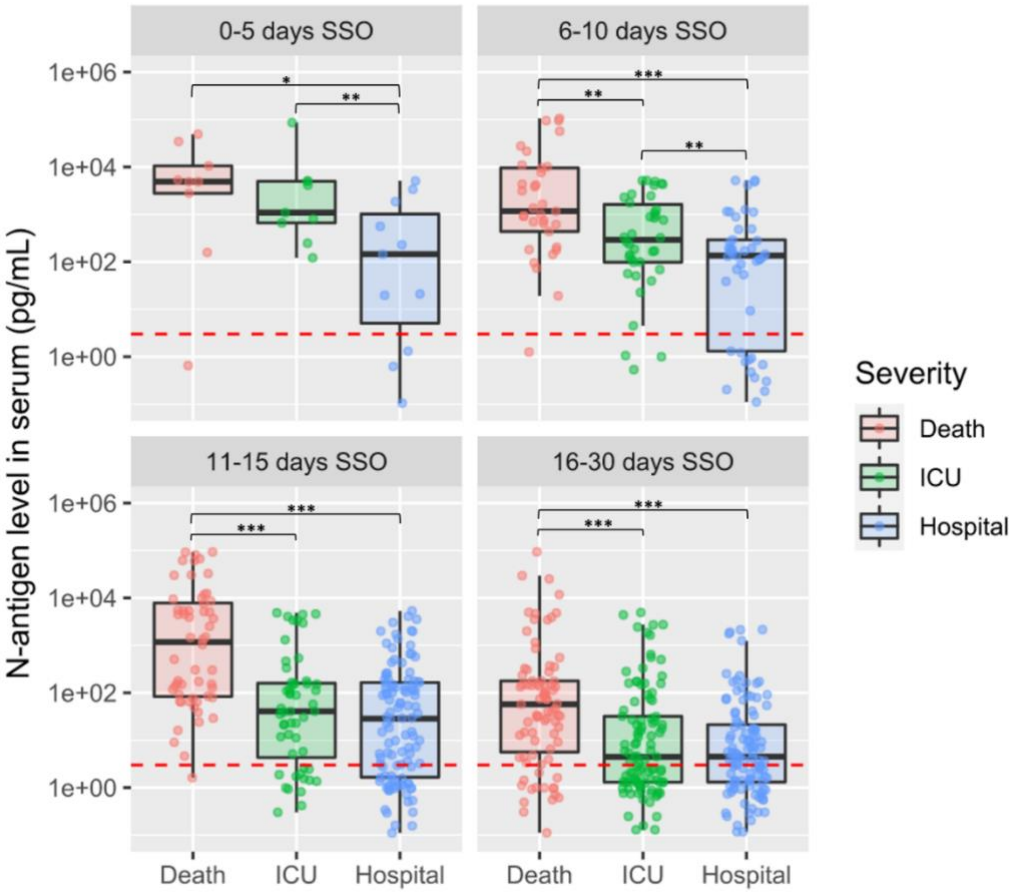

Figure 1. Distribution of N-antigen levels in serum of patients *according to the outcome (death, ICU without death or hospitalization without ICU or death) and to the delay since symptoms onset. The positivity threshold is indicated with a dashed red line.*

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Unsurprisingly, when analysing the kinetic of N-antigen and anti-N antibodies during the infection course, we observed that the N-antigen was decreasing at the time of anti-N antibodies appearance (Figure 2). However, if the levels of N-antigen were associated with disease severity, the levels of anti-N antibodies were similar accross all groups (Figure 3).

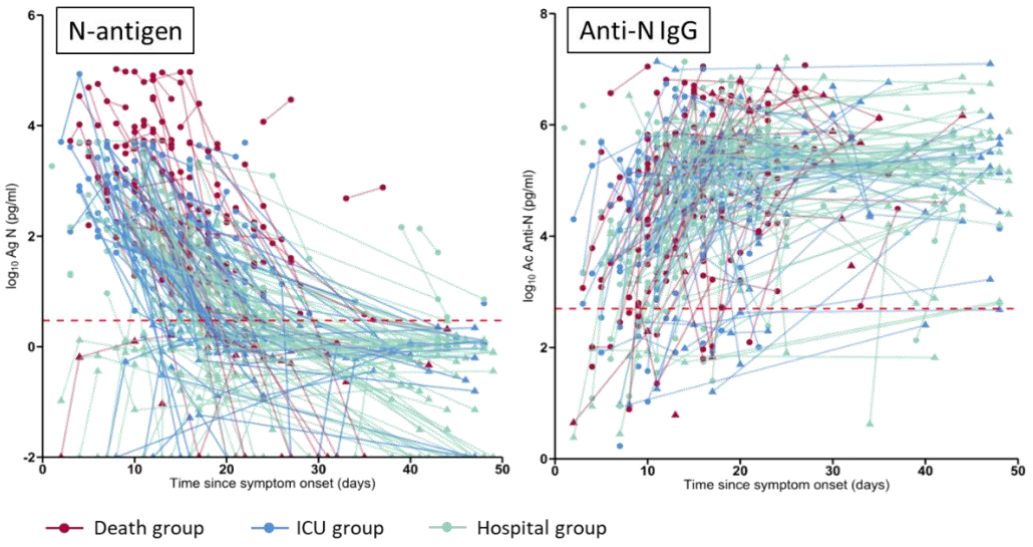

Figure 2. Spaghetti plots depicting the kinetics of N-antigen and anti-N antibodies *throughout the course of the infection according to the patients' groups.*

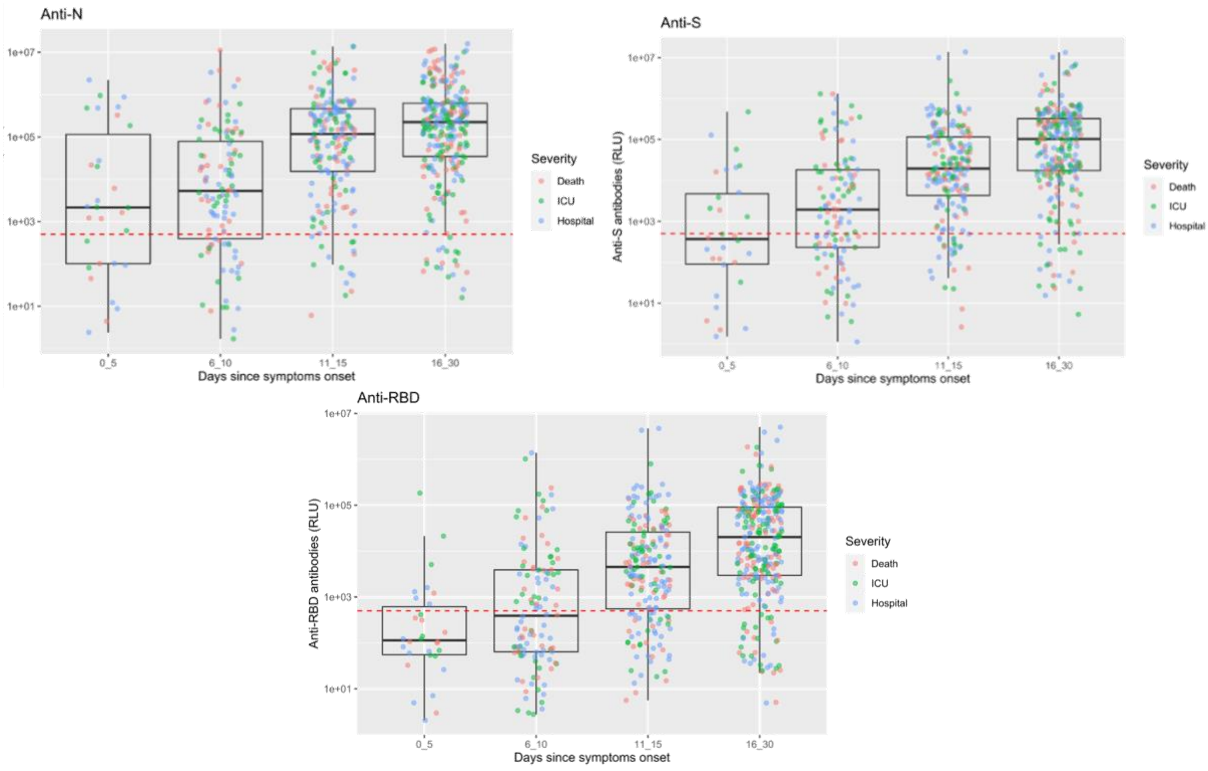

Figure 3. Kinetic of apparition of antibodies markers (anti-N, anti-S and anti-RBD) *according to disease severity and delay since symptoms onset.*

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Then, we deeper analyse the N-antibodies and N-antigen kinetics. We used a target-cell limited model with a transfer rate to the plasmatic compartment to reconstruct the viral dynamics of N-antigen concentrations with an non-linear and saturable effect of anti-N IgG on its clearance.
We estimated the basic reproduction number R0 to 13.6 and loss rate of infected cells to 0.78 d^{-1}. Infected cells were estimated to produce 3.7×10^5 viral particles per day. Viral particles were then transfered to the plasmatic compartment at a rate R equal to 10^{-4} day^{-1}.

Elimination rate of N-Antigenemia in absence of IgG was estimated at E1 = 0.13 day^{-1}, whereas the maximal elimination rate mediated by IgG was estimated at Emax=0.7 day^{-1}. This caused the half-life of N-antigen in the plasmatic compartment to decrease from 5 days to at most 0.8 days due to IgG-mediated elimination. We estimated the concentration of IgG required to achieve 50% of this effect at IgG_{50} = 2.54 AU/mL, and the maximal predicted concentration of IgG was estimated at 5.4 AU/mL.

Our model predicted N-antigenemia to peak 2.4 days after symptom onset (IQR : 1.0-6.9 days) and a median time to N-antigenemia clearance of 19.8 days after symptom onset (IQR : 17.3-23.9 days). Deceased patients' antigenemia at D8 post symptom onset was predicted significantly larger than in those discharged alive (3.31 vs 3.05 log_{10} pg/mL, respectively, P=0.0092, Figure 4) and their time of viral clearance was significantly delayed as well (23.3 vs 19.3 days post symptom onset, respectively, $P<10^{-5}$, Figure 4).

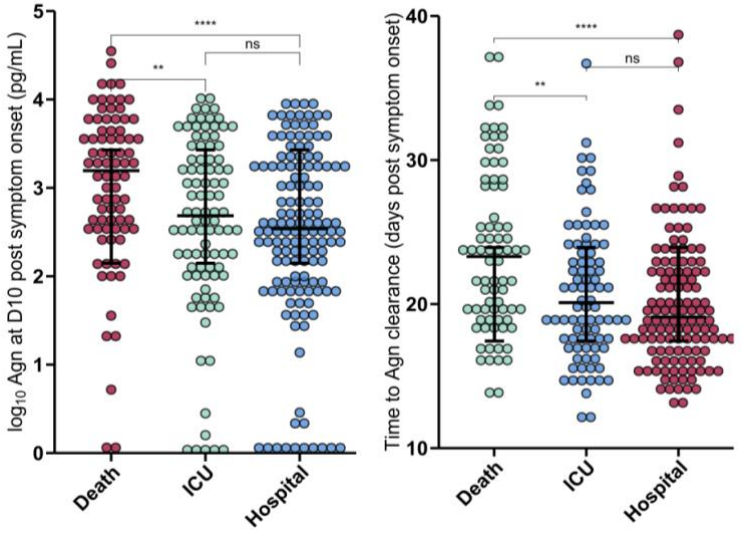

Figure 4. Modeling of N-antigen (Agn) levels at D10 post-symptom onset (left panel) and of time to N-antigen clearance (right panel) *according to disease severity groups.*

Overall, we observed a link between N-antigenemia and COVID-19 severity. Interestingly, and despite being the main driver of N-antigen disappearance in patients' blood, the anti-N antibodies were not associated to disease severity. This suggest that the antigen production is higher among death patients and, along with the longer N-antigen clearance for those patients, that a prolonged viral replication is indeed observed for dying patients. In this condition, more effort on antiviral drugs development should be made as it may help to increase viral clearance and prevent patients worsening. N-antigenemia provides a new diagnostic tool that should help to prognostic evaluation and to follow the global viral replication, and not only the nasopharyngeal viral replication on the contrary to RT-PCR on sequential NP swabs.

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