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Frequency of IgE antibody response to SARS-CoV-2 RBD protein across different disease severity COVID19 groups

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Abstract

Background COVID-19 appears to have a progression of three stages. The latter stage is characterized by a high level of cytokine release, which in turn triggers an uncontrolled reaction known as cytokine storm where mast cells are involved. The presence of anti-IgE antibodies against SARS-CoV-2 in this phase has been previously reported, suggesting an association with the severity of the disease. Our study aims to assess the prognostic significance of IgE antibodies against SARS-CoV-2 across a spectrum of clinical presentations, including individual with mild symptoms, hospitalized patients, and those who presented a critical progression.

Methods The study included 64 patients distributed into the following groups: 22 critically ill hospitalized individuals (Critical); 21 non-critical hospitalized patients (Severe); 21 mild symptomatic non-hospitalized cases (Mild); and 22 healthy blood donors with samples collected in October 2019. Anti-IgE antibodies against Spike (S) protein were detected using a homemade ELISA, where the plate was sensitized with the RBD of recombinant S protein.

Results Among 64 SARS-CoV-2 infected patients, 28.1% tested positive for IgE isotype antibodies against S protein RBD, whose prevalence was similar across severity groups: Mild 23.8%, Severe 28.6%, and Critical 31.8% ($p=0.842$). Patients with IgE response exhibited higher levels of LDH compared to non-IgE responders, with a 40% increase ($p=0.037$), and a non-significantly higher tendency in other inflammatory markers.

Conclusion In SARS-CoV-2 infection, roughly a fourth of patients presented an IgE isotype response, regardless of disease severity, which is associated with higher levels of LDH.

Keywords IgE, SARS-CoV-2, Antibody response, Prognostic factor, S protein

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Introduction

Deaths attributed to Coronavirus Disease 2019 (COVID-19) are primarily due to severe hypoxemic respiratory failure. Increasingly, studies indicate that the "cytokine storm" is the main cause of severe COVID-19 [1, 2]. This phenomenon is a cascade of heightened immune responses that can overwhelm the immune system, ultimately leading to organ failure and fatal respiratory distress [3]. COVID-19 appears to progress through three stages. The first stage is the initial infection phase (5–7 days), the second stage is the pulmonary involvement, and the third stage is the inflammatory phase (7–15 days). These latter stages are characterized by a high level of cytokine release, which triggers an uncontrollable reaction known as a cytokine storm [3, 4]. Mast cells, which are involved in the cytokine storm, play a crucial role in the development of type I hypersensitivity reactions [5–7]. This inflammatory reaction causes lung damage similar to that seen in hypersensitivity pneumonitis [8, 9].

Anti-IgE antibodies against SARS-CoV-2 have been reported, and these correlate with disease severity [10, 11]. Therefore, the detection of anti-SARS-CoV-2 IgE could play an important role in identifying patients at high risk of developing the most severe form of the disease, allowing for early application of intensive care, antivirals, or even immunotherapy to reduce complications related to this pro-inflammatory state.

One of the most immunogenic proteins of SARS-CoV-2 is the Spike (S) protein [12, 13]. The S protein is located on the surface of viral particles and contains the receptor-binding domain (RBD) through which SARS-CoV-2 interacts with angiotensin-converting enzyme 2 receptor, serving as the virus's entry point [14]. The proposed study aims to evaluate whether the abundance of serum IgE antibodies bound to the S protein —specifically directed against the RBD region— is associated with severe COVID-19, and its potential utility as a marker for disease severity and prognosis.

Methods

Ethical issues

This study has been reviewed and approved by the Ethics and Drug Research Committee of Parc Taulí University Hospital. All patients included have signed a consent form to participate in the study.

Patients The study included a total of 87 individuals distributed across the following groups: Critical Group: 22 COVID-19 patients hospitalized due to severe manifestations of the infection who progressed to a critical condition before ultimately recovering and being discharged. Criteria for critical progression were defined a priori and included clinical features such as a respiratory rate ≥ 30 breaths per minute with a PaO2 < 94% on FiO2 ≥ 0.35, a PaO2/FiO2 ratio < 200, or the need for non-invasive mechanical ventilation or orotracheal intubation. Severe Group: 21 COVID-19 patients hospitalized due to severe disease who did not progress to a critical condition. These patients were admitted to the Parc Taulí University Hospital (PTUH) for severe manifestations of the disease but maintained stable conditions throughout their hospitalization. Mild Group: 21 COVID-19 patients with mild symptoms who were evaluated in the emergency department of PTUH and were not hospitalized during the course of their illness. Healthy Controls: 23 healthy individuals with no prior exposure to SARS-CoV-2. Blood samples from this group were obtained from donors at the Banc de Sang i Teixits in October 2019, prior to the onset of the pandemic. The demographic characteristics of the patients selected for the study are presented in Table S1. The patient samples were obtained from the I3PT Biobank, whereas the healthy donor samples were provided by the Banc de Sang i Teixits of Barcelona. The latter correspond to specimens collected in October 2019, five months prior to the detection of the first SARS-CoV-2 case in Barcelona. At the time of sample collection, none of the subjects had been vaccinated against SARS-CoV-2, and their current infection constituted their first exposure to the virus.

Determination of anti-RBD SARS-CoV-2 IgE levels using ELISA IgE anti-RBD levels were detected using an in-house ELISA in Triturus analyzer (Grifols, Barcelona, Spain). Immulon 4 HBX plates (Nunc, Thermo Fisher Scientific, Waltham, MA, USA) were coated with 10 µg/mL of recombinant RBD (Thermo Fisher Scientific, Waltham, MA, USA) in 50 mM carbonate-bicarbonate buffer (pH 9.6) and incubated overnight at 4 °C. The plates were then blocked with 5% PBS-BSA (Sigma-Aldrich, St. Louis, MO, USA) for 2 h at room temperature. Subsequently, individual serum samples were diluted 1:4 in PBS-Tween 20® 0.05% (Sigma-Aldrich, St. Louis, MO, USA) and incubated for 1 h at room temperature. The ELISA plates were washed three times with 250 µL of PBS-Tween 20® 0.05%. After washing, HRP-conjugated anti-human IgE-ε chain (Thermo Fisher Scientific, Waltham, MA, USA) diluted 1:1,000 in PBS-Tween 20® 0.05% was added and incubated for 1 h at room temperature. Then, the ELISA plates were washed three times with 250 µL of PBS-Tween 20® 0.05%. After washing, the enzymatic reaction was developed using tetramethylbenzidine (Thermo Fisher Scientific, Waltham, MA, USA) at room temperature for 30 min and stopped with 25% sulfuric acid (Merck, Darmstadt, Germany). Absorbance was measured at 450 nm, with 620 nm as the reference filter. The cutoff value was determined ensuring 95.4% specificity for prepandemic blood donors.

Statistical analysis

For descriptive purposes, demographic and clinical features were summarized using medians and ranges for continuous variables, while absolute and relative frequencies were used for categorical variables. Differences between patient groups were assessed using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables.

Quantitative differences in Anti-RBD IgE antibody titers between patient groups were evaluated using a linear model, with age, sex, and days from the onset of clinical symptoms to sample collection included as covariates for statistical control. To meet the assumptions of the model, the response variable was transformed using the most appropriate Box-Cox transformation ($\lambda = 0.25$). Adjusted group means were derived from the model and back-transformed to the original response scale. Fold changes (FC) were calculated from these adjusted means to quantify differences between groups relative to controls and for pairwise comparisons. Statistical significance for these comparisons was assessed using Wald's test for the respective linear contrasts, and 95% confidence intervals (CIs) were calculated via parametric bootstrapping from the model coefficients.

For qualitative analysis, individuals were classified as IgE responders if their titer exceeded a threshold of 0.542, established to ensure 95% assay specificity based on levels observed in healthy donors. Differences in the proportion of IgE responders across patient severity groups were assessed using a Chi-square test, and 95% CIs for each group proportion were calculated with the Clopper-Pearson method.

Finally, the association between IgE responder status and various analytical or clinical parameters was tested using two approaches. For numerical responses, such as analytical parameters, linear models were used to assess differences between IgE responder groups, adjusting for sex and age. The response variable was transformed with the most appropriate Box-Cox transformation to satisfy model assumptions. Adjusted means for each IgE responder group were derived from these models, and group differences were tested using Wald's test for the respective model coefficients. For categorical responses, such as comorbidities or treatments, logistic regression models were fitted with IgE responder group as the main predictor, adjusting for sex and age. Due to low counts in positive responses, effect estimation was not feasible, and associations with IgE response were instead tested using likelihood ratio tests.

Statistical significance was set at a 5% threshold. All analyses and visualizations were conducted using R 4.1.2 (R Core Team, 2021. R: A language and environment for statistical computing. R Foundation for Statistical).

Results

Anti-RBD IgE in SARS-CoV-2 patients across different severity groups

The study involved 64 patients distributed into the following groups: 22 critically ill hospitalized individuals (Critical); 21 non-critical hospitalized patients (Severe); 21 mild symptomatic non-hospitalized cases (Mild); and 22 healthy blood donors with samples collected in October 2019. Demographic, clinical, and laboratory data were collected from these patients (Table 1, Supplemental Fig. 1).

The presence of IgE isotype antibodies against various SARS-CoV-2 proteins, including the RBD, has been previously reported [10, 15]. Anti-IgE antibodies against Spike (S) protein were detected using a homemade ELISA, where the plate was sensitized with 1 µg/well of recombinant RBD (S protein) (Thermofisher Scientific, Waltham, MA, USA) and patient serum was diluted 1:4 in PBS-Tween20 0.05%. The cutoff point was established to achieve an assay specificity of 95.4% based on levels observed in healthy donors. Among 64 SARS-CoV-2 infected patients, 28.1% tested positive for IgE isotype antibodies against RBD protein, whose prevalence was similar across severity groups: Mild 23.8%, Severe 28.6%, and Critical 31.8%, $p = 0.842$ (Table 2).

Table 1 Descriptive statistics of patients included in the study

		Total *N* = 86	Control *N* = 22 (25.6%)	Mild *N* = 21 (24.4%)	Severe *N* = 21 (24.4%)	Critical *N* = 22 (25.6%)	*P*-value
Sex	**Male**	45 (52. %)	9 (40.9%)	11 (52. %)	13 (61. %)	12 (54. %)	0.588
	Female	41 (47. %)	13 (59.1%)	10 (47. %)	8 (38. %)	10 (45. %)	
Age (years)		52.5 [19.0, 91.8]	43.0 [19.0, 58.0]	49.9 [20.0, 82.7]	61.7 [21.3, 91.8]	60.8 [25.8, 84.4]	**0.001**
Anti-RBD IgE antibody titers		0.21 [0.00, 3.34]	0.20 [0.00, 0.55]	0.11 [0.00, 1.17]	0.27 [0.00, 2.03]	0.28 [0.00, 3.34]	0.329
Days from first clinical symptoms to sample extraction		7.0 [0.0, 38.0]	-	4.0 [0.0, 20.0]	7.0 [0.0, 15.0]	9.0 [0.0, 38.0]	**0.039**

Table 2 ELISA IgE positive for SARS-CoV-2 infected patients

	Total *N* = 64	IgE negative *N* = 46	IgE positive *N* = 18	Positivity rate [95%CI]	*P*-value
Mild	21	16	5	0.238 [0.082,0.472]	0.842
Severe	21	15	6	0.286 [0.113,0.522]	
Critical	22	15	7	0.318 [0.139,0.549]	

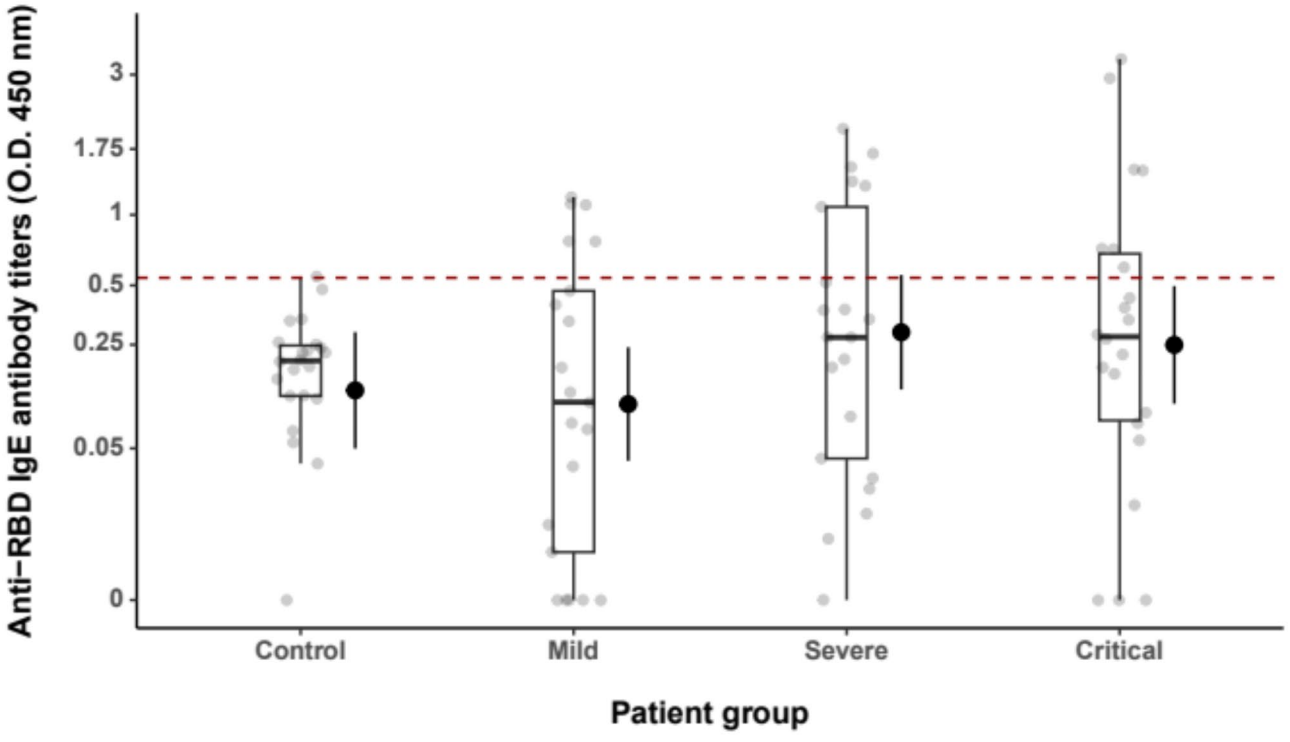

Fig. 1 Anti-RBD IgE antibody titers quantified using an in-house ELISA. Boxplots illustrate the distribution of peptide quantification. Whiskers extend 1.5 times the interquartile range (IQR) from each end of the box. Point-range symbols represent the adjusted group means of protein titers after statistical control for confounders, and their extension represents the 95% confidence intervals. These estimates were derived from a linear model and adjusted for sex, age and days from first clinical symptoms to sample extraction, in which Anti-RBD IgE antibody titer quantifications were transformed using the most suitable Box-Cox transformation with a lambda value of 0.25 in order to fulfill model assumptions. The red dashed line represents the threshold for ELISA positivity set to achieve a 95% assay specificity in the group of healthy controls

In our quantitative analysis adjusted for age, sex and days from the onset of clinical symptoms to sample collection, the median values for the mild patient group were 0.108 (0.039, 0.242), for the severe group 0.292 (0.135, 0.558), and for the critical group 0.249 (0.108, 0.497) (Fig. 1 and Table S1). The fold change (FC) for the comparison between mild and severe groups was 2.71 (-1.27, 9.28; $p = 0.083$), while between mild and critical groups it was 2.31 (-1.27, 7.59; $p = 0.166$) (Table S2). However, when comparing with the control group, the difference decreased to 2.19 (-1.52, 5.75; $p = 0.175$) for the severe group and 1.87 (-1.42,6.91; $p = 0.297$) for the critical group (Table S2).

Anti-RBD IgE SARS-CoV-2 and clinical characteristics

Finally, we conducted an analysis of the various analytical and clinical parameters recorded for the patients, classifying them based on the presence of an IgE response. We observed that IgE responders had higher levels of inflammatory markers, with a statistically significant 40% increase in LDH levels in this group, $p = 0.037$ (Table 3).

Regarding clinical parameters, IgE responders were more frequently treated with Remdesivir (25% vs. 4%), and the use of Tocilizumab was twice as high, although only the former reached statistical significance ($p = 0.042$) (Table 4). Conversely, obesity, dyslipidemia, and the need for intensive care were twice as common in non-IgE responders, with a statistically significant difference observed in dyslipidemia, $p = 0.047$ (Table 4).

Table 3 Analytical characteristics among SARS-CoV-2 infected patients by IgE response status

	***N* available** ***N*=64**	**Non IgE responders** ***N*=46 (71.9%)**	**IgE responders** ***N*=18 (28.1%)**	***P*-value**
Lymphocytes (x10^{9}cells /L)	62	1213.7 [998.6, 1449.8]	1459.8 [1098.5, 1872.4]	0.267
Neutrophils (x10^{9}cells /L)	62	4757.5 [3980.5, 5603.8]	4950.6 [3740.2, 6330.4]	0.801
Leukocytes (x10^{9}cells /L)	62	6035.8 [5073.7, 7081.4]	7923.6 [6226.6, 9824.9]	0.064
Ferritin (ng/mL)	58	548 [387.2, 754.2]	671.7 [397.5, 1067.8]	0.499
CRP (mg/dL)	59	4.8 [3.2, 7.1]	7.8 [4.3, 13.1]	0.178
LDH (U/L)	53	274.8 [231.5, 326.1]	383.9 [295.7, 498.3]	**0.037**
D Dimer (ng/mL)	54	616.3 [477.9, 808.5]	814.2 [556.9, 1238.9]	0.241

CRP: C-reactive protein; **LDH**: Lactate dehydrogenase

Table 4 Clinical characteristics among hospitalized SARS-CoV-2 infected patients by IgE response status

	***N* available** ***N*=40**	**Non IgE responders** ***N*=28 (70.0%)**	**IgE responders** ***N*=12 (30.0%)**	***P*-value**
Diabetes Mellitus	40	4 (14.3%)	3 (25.0%)	0.6310
Obesity	40	10 (35.7%)	2 (16.7%)	0.1820
Dyslipidemia	40	5 (17.9%)	1 (8.3%)	**0.0467**
Arterial hypertension	40	8 (28.6%)	3 (25.0%)	0.1740
Corticosteroids treatment	39	23 (85.2%)	11 (91.7%)	0.5750
Remdesivir treatment	40	1 (3.6%)	3 (25.0%)	**0.0421**
Tocilizumab treatment	40	5 (17.9%)	4 (33.3%)	0.4330
NIV	40	11 (39.3%)	3 (25.0%)	0.2960
Intensive care needs	40	9 (32.1%)	2 (16.7%)	0.2760

NIV: Non-invasive mechanical ventilation

Discussion

The present study analyzes the IgE response to the RBD of SARS-CoV-2 in patients classified according to the severity of their infection. Plüme et al.'s study showed that the prevalence of IgE varies from 2.9 to 82.6%, depending on the target peptide. Specifically, the prevalence of antibodies against the RBD in Plüme's study is 2.9%, whereas in our study it is 28% [10]. This difference might be attributed to the detection technology, particularly the antigen used: Plüme et al. employ a peptide, while we use the full domain. However, the study by Portilho et al. [16], which examines IgE against the RBD using an ELISA system, reports a similar prevalence of 23% in patients with SARS-CoV-2 infection. Another study examining IgE antibody prevalence is that of de Sousa et al. [15], which employs the same methodology as ours but with a different antigen source, utilizing the trimeric S protein. In their study, the prevalence is 2.6%, considerably lower than in ours. This discrepancy may be due to the method of determining the cut-off point: while de Sousa et al. use optical density plus three times the standard deviation, we set the specificity for the ELISA at 95.4% with normal controls.

Some studies suggested a correlation between the presence of IgE antibodies against SARS-CoV-2 and the severity of infection [10, 11]. In Plüme's study, a significantly higher amount of these antibodies targeting the nucleocapsid protein peptides of SARS-CoV-2 is observed in patients with greater severity. Similarly, Tan et al., using the S1 protein as an antigen, also report

higher levels of IgE against SARS-CoV-2 in the group of severely ill patients. Both studies perform this analysis quantitatively. These results might suggest a usefulness of IgE detection response among symptomatic SARS-CoV-2 subjects in identifying those at higher risk of admission. In this sense, although the qualitative analysis of the association between the presence of IgE response and disease severity indicates that no such relationship exists, our quantitative data show a slight, non-significant trend indicating the opposite. This trend has also been observed in studies by Plüme et al. and Tan et al., which conducted similar investigations at a quantitative level [10, 11]. However, given the discrepancy between qualitative and quantitative analyses, we understand that measuring the total reactivity detected in the ELISA system, which falls below the cutoff point for establishing this association, has limited clinical relevance. Another factor that may explain the differences with the studies by Plümme and Tan is the antigenic source used to detect IgE isotype antibodies. In Plümme's study, the antigens associated with severity include the full-length S protein, the S1 subunit of the S protein, and the full-length nucleocapsid protein. In this study, as in ours, no correlation with COVID-19 severity was observed when using the RBD domain of the S protein. In contrast, Tan's study employs the S1 subunit of the spike protein and the nucleocapsid protein as antigens. Our findings, based on the use of RBD as the antigen and our patient cohort, suggest that there might not be a correlation between the IgE response to SARS-CoV-2 RBD protein and the severity of the disease.

As expected, the presence of IgE in our patient cohort increases the levels of inflammatory markers due to the additional activation of mast cells ([6, 17, 18]), leading to more frequent use of anti-inflammatory and antiviral therapies (Table 3). Interestingly, ICU admission is more common among non-IgE responders, which contradicts the association between IgE and disease severity found in the studies by Plüme and Tan [10, 11]. Mast cell activation, in conjunction with other factors, can trigger the cytokine storm that leads to the need for ICU admission [6, 7, 19]. However, based on the results we obtained, the lack of correlation between IgE and disease severity—despite its presence with similar prevalence across all severity groups—and the higher ICU admission rates in patients who do not respond with IgE suggest that mast cell activation might not be a central factor in the cytokine storm observed in SARS-CoV-2 infection. While mast cell activation may contribute to a more pronounced inflammatory response, it does not appear to be the primary trigger of the cytokine storm. An alternative explanation is that mast cell activation may indeed play a crucial role in the pathophysiology of the cytokine storm in SARS-CoV-2 infection, but the key factor may not be IgE-mediated activation. Instead, other processes—such as complement factors, stem cell factor, neuropeptides, and other inflammatory mediators—may independently activate mast cells [20, 21], which could explain the homogeneous prevalence of IgE response across different severity groups. Thus, the observation of a higher ICU admission requirement in non-IgE responders aligns with the lack of association between IgE response and COVID-19 severity in our patient cohort.

In conclusion, we observed a homogeneous IgE anti-SARS-CoV-2 response across different severity groups of patients in the studied cohort, with a trend indicating an association with higher levels of inflammatory parameters, particularly LDH. However, these results suggest limitations in its potential clinical application as a biomarker of severity.

Abbreviations

COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
S	Spike
RBD	Receptor binding domain
LDH	Lactate dehydrogenase
FC	Fold change
CRP	C-reactive protein
LDH	Lactate dehydrogenase
NIV	Non-invasive mechanical ventilation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02677-y.

Supplementary Material 1

Supplementary Material 2

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Author contributions

JFD has participated in conceptualization, methodology, validation, formal analysis, data curation and original draft preparation. ARP has participated in methodology, formal analysis, data curation and original draft preparation. IAC has participated in investigation and validation. IBB has participated in investigation and validation. JGM has participated in review manuscript and supervision. ABL has participated in conceptualization, methodology and review manuscript. JCF has participated in resources, review and editing manuscript and supervision.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study has been reviewed and approved by the Ethics and Drug Research Committee of Parc Taulí University Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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