DOI: 10.4274/gulhane.galenos.2023.04834
Gulhane Med J 2023;65:145-151

Can pre-treatment inflammatory biomarker levels predict the response of tocilizumab therapy in COVID-19 patients?

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Date submitted:
17.11.2022
Date accepted:
14.04.2023
Online publication date:
15.12.2023

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Keywords: COVID-19, tocilizumab, prognostic nutritional index, C-reactive protein/albumin ratio, systemic immune-inflammatory index

ABSTRACT

Aims: The results of randomized clinical trials evaluating the effects of tocilizumab in patients with patients are inconsistent. We aimed to investigate the reliability of pre-treatment levels of prognostic nutritional index (PNI), C-reactive protein (CRP)/albumin ratio (CAR), systemic immune-inflammatory index (SII), interleukin-6 (IL-6), and lactate dehydrogenase (LDH) as treatment response biomarkers in hospitalized coronavirus disease-2019 (COVID-19) patients who were administered tocilizumab.

Methods: Adult patients hospitalized for COVID-19 confirmed by severe acute respiratory syndrome-coronavirus-2 polymerase chain reaction and administered tocilizumab because of rapid clinical worsening despite receiving standard care were retrospectively included. Patients who received steroids, anakinra, or IVIG before tocilizumab and had missing data were excluded. Treatment effectiveness was evaluated with the improvement in the clinical status on an eight-category ordinal scale at 28 days of tocilizumab administration.

Results: One hundred and thirty-three COVID-19 patients with a mean age of 62.64±13.66 years and consisting of 93 (69.9%) males were included. At 28 days of tocilizumab administration, 99 (74.4%) patients improved. Improved patients after tocilizumab treatment had significantly lower IL-6, LDH, SII, CAR, and higher PNI. To predict the effectiveness of tocilizumab, IL-6 had the highest area under the curve (AUC) value (AUC=0.782), followed by LDH (AUC=0.761), PNI (AUC=0.696), SII (AUC=0.671), CAR (AUC=0.682), and CRP (AUC=0.643). The cut-off level was 143.12 pg/mL for IL-6 (sensitivity=84.85%, specificity=64.71%), 460U/L for LDH (sensitivity=71.72%, specificity=73.75%), 31.35 for PNI (sensitivity=79.80%, specificity=55.88%), 3895.92 for SII (sensitivity=90.91%, specificity=47.06%), and 61.15 for CAR (sensitivity=67.68%, specificity=61.76%).

Conclusions: In COVID-19 patients with clinically worsening disease, the administration of tocilizumab in the early stage of the hyperinflammatory state may improve the prognosis. Pre-treatment inflammatory biomarker levels may predict tocilizumab response.

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection may cause various clinical manifestations ranging from asymptomatic to multisystem life-threatening manifestations (1). Although most patients experience only mild to moderate symptoms, a subgroup of patients may progress to severe and critical disease, including Acute respiratory distress syndrome (ARDS), multi-organ failure, and death. Although the pathogenesis of coronavirus disease-2019 (COVID-19) is considered to result from a complex interplay of multiple pathophysiological mechanisms, such as direct viral effect, renin–angiotensin–aldosterone system imbalance, dysregulated immune response, and coagulopathy, an overproduction of pro-inflammatory cytokines, described as cytokine storm, is considered as a major reason for disease progression and death (2,3).

The pleiotropic cytokine interleukin-6 (IL-6) plays a pivotal role in the pathogenesis of COVID-19, and circulating levels of IL-6 are closely associated with clinical outcomes (4,5). Therefore, tocilizumab, an inhibitor of IL-6 receptors, was considered an attractive therapeutic option. However, the results of randomized clinical trials that evaluated the effects of tocilizumab in patients with COVID-19 are inconsistent because of the differences in trial design, initial disease severity used for the inclusion or exclusion, timing of tocilizumab administration, use of co-interventions, and outcome measurements (6).

The prognostic nutritional index (PNI), C-reactive protein (CRP)/albumin ratio (CAR), and systemic immune-inflammatory index (SII), which are novel parameters for measuring the degree of inflammation, have been reported as valuable biomarkers for discriminating disease severity and predicting mortality in COVID-19 (7-15).

As tocilizumab treatment may be beneficial in some SARS-CoV-2-infected patient populations, the ideal patient group and optimal timing for tocilizumab administration are still unknown. Thus, determining the patient populations likely to benefit from tocilizumab is important. In this study, we evaluated the reliability of pre-treatment levels of PNI, CAR, SII, IL-6, and lactate dehydrogenase (LDH) as treatment response biomarkers in hospitalized COVID-19 patients who were administered tocilizumab.

Methods

Study design and participants

This retrospective study was conducted at the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Ankara, Türkiye. The study protocol was first registered in the data of the Türkiye Republic Ministry of Health Scientific Research Committee and then approved by the Committee on the Human Research Ethics of the University of Health Sciences Türkiye, Gülhane Faculty of Medicine (date: 26.05.2021, number: 2021/35). The study was conducted in accordance with the Declaration of Helsinki. Between May 1 and September 1, 2020, consecutive SARS-CoV-2-infected patients who consulted the rheumatology department because of rapid clinical worsening were evaluated for inclusion. Electronic medical records of the patients were used to collect data.

The inclusion criteria were as follows: (1) age ≥18 years, (2) positive nasopharyngeal swab reverse-transcriptase-PCR for SARS-CoV-2 RNA, and (3) chest computed tomography (CT) findings suggestive of COVID-19. The exclusion criteria were as follows: (1) patients who received steroids, anakinra, or IVIG before tocilizumab administration and (2) patients with missing baseline data.

A total of 133 patients who received tocilizumab were included in the study. Demographic, clinical, laboratory, and treatment data were obtained from the patient's medical records. The clinical status before tocilizumab administration was assessed according to the eight-category ordinal scale (16).

Category 1: Non-hospitalized patients with no activity restrictions.

Category 2: Hospitalized patients with limited activities and/or home oxygen requirements.

Category 3: Hospitalized patients not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons).

Category 4: Hospitalized patients who do not require supplemental oxygen but need ongoing medical care related to COVID-19 or other medical conditions.

Category 5: Hospitalized patients because of the need for supplemental oxygen.

Category 6: Hospitalized patients because of the need for noninvasive ventilation or use of high-flow oxygen devices.

Category 7: Patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation.

Category 8: Death.

Treatment protocol

The treatment protocol of the Turkish Ministry of Health for COVID-19 was recorded in the patient files. The protocol of the period included hydroxychloroquine (±azitromycin) for 5-10 days and venous thromboembolism prophylaxis in the absence of a major contraindication. When clinical evidence of progressive COVID-19 was observed despite this standard care (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L), available sets of recommendations included the use of single-dose tocilizumab 8 mg/kg (maximum dose: 800 mg) after exclusion of bacterial and fungal co-infection. A second dose was recommended when no improvement was observed after the first dose within 24 hours.

Outcome

The end-points were improvement in the clinical status on an eight-category ordinal scale at 28 days of tocilizumab administration. The patients were divided into two groups: those who improved after tocilizumab therapy and those who did not. Serum alanine transaminase, aspartate transaminase, LDH, urea, creatinine, CRP, albumin, ferritin, fibrinogen, IL-6 levels, and complete blood count were available for all patients. Laboratory results in the last 24 hours before tocilizumab administration were used to calculate PNI, SII, and CAR. PNI was calculated as serum albumin levels (g/L) + 5 total lymphocyte count (10^9/L) (17). SII was determined using the following formula: platelet count neutrophil count/lymphocyte count (18). CAR was obtained by dividing the CRP levels by albumin level (19).

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA) 16.0 program for Windows. Histograms, probability plots, and the Kolmogorov-Smirnov test were used to check the normal distribution. Normally distributed variables were expressed as mean±standard deviation, skewed variables as median (interquartile range) (25^{th} and 75^{th} percentiles), and categorical variables as number and percentage. The performance of IL-6, CAR, PNI, SII, and LDH in predicting the response to tocilizumab was analyzed using receiver operating characteristic curve analysis. The Youden index was used to determine the best cut-off values for these biomarkers. When a significant cut-off value was observed, the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A test with an area under the curve (AUC) of ≥0.85 was considered accurate. P<0.05 was considered statistically significant.

Results

The study included 132 patients who received tocilizumab treatment because of clinical progression and cytokine storm despite standard care. The clinical characteristics and laboratory findings of the study groups are shown in Table 1. Overall, the patients were predominantly male (69.9%) with a mean age of 62.64±13.66 (range, 22-90 years) years. Eighty-eight (66.2%) patients had at least one comorbid disease, and the most common comorbidity was hypertension (35.3%), followed by diabetes mellitus (31.6%). The frequency of concomitant antibiotic therapy and steroids was similar between the groups.

Patients who improved after tocilizumab therapy (n=99, 74.4%, were significantly younger and had significantly lower IL-6, LDH, SII, CAR, and higher PNI than patients who did not improve (Table 1).

Table 1. Clinical characteristics of the study sample

	Patients who improved (n=99)	Patients who died (n=34)	p-value
Age, mean±SD, years	60.57±13.81	68.68±11.35	**<0.001**
Male sex, n (%)	74 (73.7)	19 (55.9)	0.380
Time from symptom onset to tocilizumab treatment, days, median (IQR)	9.0 (7.0-11.0)	9.5 (6.0-12.3)	0.824
Clinical status, n (%)			**<0.001**
Category 4	6 (6.1)	0	
Category 5	77 (77.8)	6 (17.6)	
Category 6	15 (15.2)	13 (38.2)	
Category 7	1 (1)	15 (44.1)	
Comorbidities, n (%)			
Hypertension	28 (28.3)	19 (55.9)	**0.006**
Diabetes mellitus	27 (27.3)	15 (44.1)	0.087
Intermediate or advanced chronic kidney disease	6 (6.1)	7 (20.6)	**0.021**
Coronary artery disease	19 (19.2)	8 (23.5)	0.587
Congestive heart failure	4 (4)	5 (14.7)	**0.047**
Hyperlipidemia	2 (2)	1 (2.9)	0.755
Treatment, n (%)			
Antibiotic treatment	79 (79.8)	30 (88.2)	0.270
Steroid after tocilizumab administration	12 (12.1)	6 (17.6)	0.416
Laboratory parameters at tocilizumab administration			
White blood cell count (x10^3/μL), median (IQR)	6.70 (5.00-8.30)	9.10 (6.20-11.83)	**<0.001**
Lymphocyte count (x10^3/μL), median (IQR)	0.80 (0.60-1.10)	0.55 (0.40-0.93)	**0.016**
Neutrophil count (x10^3/μL), median (IQR)	5.10 (3.70-6.70)	8.30 (5.03-10.60)	**<0.001**
Platelet count, (x10^3/μL), median (IQR)	230.00 (188.00-280.00)	218.00 (156.25-306.25)	0.400
LDH (U/L), median (IQR)	392.00 (317.00-480.00)	586.50 (414.750-772.00)	**<0.001**
IL-6 (pg/mL), median (IQR)	80.44 (54.97-124.10)	168.26 (103.40-284.47)	**<0.001**
CRP (mg/L), median (IQR)	146.20 (102.40-210.46)	198.15 (139.91-264.00)	**0.013**
Fibrinogen (mg/dL), median (IQR)	636.00 (514.00-769.00)	688.00 (513.00-867.00)	0.407

Table 1. Continued

	Patients who improved (n=99)	Patients who died (n=34)	p-value
D-dimer (mg/L), median (IQR)	0.78 (0.48-1.24)	1.98 (1.18-3.91)	**<0.001**
Albumin (g/dL), median (IQR)	3.07 (2.81-3.35)	2.79 (2.56-3.01)	**<0.001**
CAR, median (IQR)	48.41 (34.67-71.39)	67.90 (45.69-96.54)	**0.002**
PNI, median (IQR)	34.90 (31.90-38.70)	30.95 (26.95-36.50)	**0.001**
SII, median (IQR)	1548.00 (814.77-2692.57)	3167.13 (1111.83-7162.13)	**0.003**

SD: Standard deviation, n: Number, IQR: Interquartile range, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio, PNI: Prognostic nutritional index, SII: Systemic immune-inflammatory index

To predict the response to tocilizumab treatment, IL-6 had the highest AUC value [AUC=0.782, 95% confidence interval (CI): 0.694-0.870], followed by LDH (AUC=0.761, 95% CI: 0.661-0.861), PNI (AUC=0.696, 95% CI: 0.584-807), SII (AUC=0.671, 95% CI: 0.551-0.790), CAR (AUC=0.682, 95% CI: 0.578-0.786), and CRP (AUC=0.643, 95% CI: 0.535-0.751) (Figure 1). A cut-off level of 143.12 pg/mL for IL-6 had 84.85% sensitivity and 64.71% specificity, 460 U/L for LDH had 71.72% sensitivity and 73.75% specificity, 31.35 for PNI had 79.80% sensitivity and 55.88% specificity, 3895.92 for SII had 90.91% sensitivity and 47.06% specificity, and 61.15 for CAR had 67.68% sensitivity and 61.76% specificity. The performance of these markers in predicting the effectiveness of tocilizumab therapy is shown in Table 2.

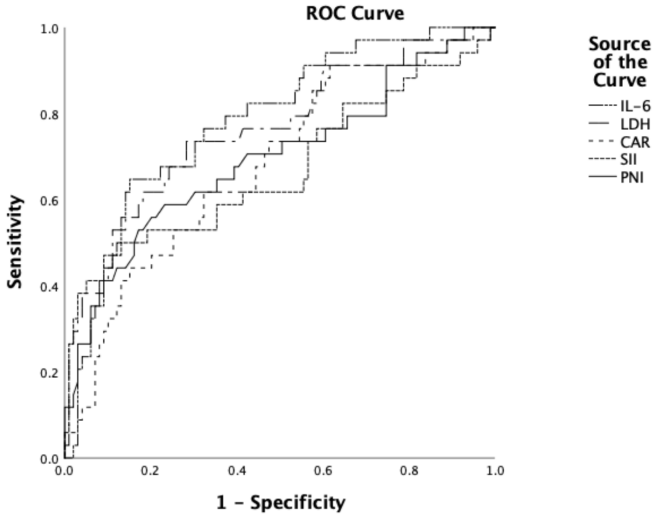

Figure 1. ROC curves of IL-6, LDH, CAR, SII and PNI

IL-6: Interleukin-6, LDH: Lactate dehydrogenase, CAR: C-reactive protein/albumin ratio, SII: Systemic immune-inflammatory, PNI: Prognostic nutritional index, ROC: Receiver operating characteristic

Discussion

To the best of our knowledge, this is the first study to assess the predictive value of PNI, CAR, and SII in determining the response to tocilizumab treatment in patients with COVID-19. Among 133 patients with COVID-19, approximately three-quarters of patients improved after tocilizumab therapy and those had significantly lower IL-6, LDH, SII, CAR, and significantly higher PNI compared with those who failed to receive tocilizumab therapy. To predict the effectiveness of tocilizumab in COVID-19 patients, serum IL-6 level had the highest AUC value, followed by LDH, PNI, CAR, SII, and CRP.

In severe COVID-19, cytokine storm syndrome, an overproduction of proinflammatory cytokines and overactivation of immune cells, can lead to life-threatening medical syndromes including disseminated intravascular coagulation, ARDS, multiorgan failure, and even death if treatment is inadequate (20). Therefore, the timing of diagnosis and treatment are very important strategies for COVID-19 management. Among the cytokines, IL-6 has received particular attention for its relation to COVID-19. The association between IL-6 levels and disease severity has been reported in several studies. Therefore, IL-6 blockade was postulated as an effective therapeutic strategy to reduce inflammation in the cytokine storm associated with COVID-19, and attention was focused on tocilizumab, a recombinant monoclonal antibody against the IL-6 receptor.

Table 2. Predictive performance of inflammatory biomarkers in predicting effectiveness after tocilizumab therapy

	Sensitivity (%)	Specificity (%)	PLR	NLR	PPV (%)	NPV (%)	Accuracy (%)	DOR
IL-6 <143.12 pg/mL	84.85	64.71	2.40	0.23	87.50	59.46	79.70	10.27
LDH <460 U/L	71.72	73.75	2.71	0.38	88.75	57.18	72.18	7.04
PNI >31.35	79.80	55.88	1.88	0.36	84.04	48.72	73.68	5.00
SII <3895.92	90.91	47.06	1.72	0.19	83.33	64.00	79.70	8.89
CAR <61.15	67.68	61.76	1.77	0.52	83.75	39.62	66.17	3.38

IL-6: Interleukin-6, LDH: Lactate dehydrogenase, PNI: Prognostic nutritional index, SII: Systemic immune-inflammatory index, CAR: C-reactive protein/albumin ratio, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, DOR: Diagnostic odds ratio

Although early observational studies have indicated improved outcomes in COVID-19 patients who received tocilizumab, subsequent randomized clinical trials assessing tocilizumab efficacy reported conflicting results (21-24). However, these trials differed considerably in patient number, study design, disease severity contents of the applied standard of care therapy, and concomitant steroid dosage. Consequently, the benefit of tocilizumab treatment in some patient groups cannot be denied. In this context, we aimed to perform the current study because it was timely and important to define the patients who will benefit from tocilizumab or not, and determine the optimal timing of tocilizumab therapy to prevent drug-related side effects and increase in costs due to unnecessary drug use.

Regarding the reliability of IL-6 as a treatment response biomarker in patients with COVID-19, Flisiak et al. (25) reported that tocilizumab administration reduced mortality and accelerated clinical recovery in patients with pre-treatment IL-6 levels higher than 100 pg/mL who required supplemental oxygen. On the other hand, Li et al. (26) reported that pre-treatment IL-6 levels equal to or higher than 100 pg/mL were associated with poor prognoses after tocilizumab therapy. Similar to the study by Li et al. (26), in our study, serum IL-6 levels were significantly lower in patients who improved after tocilizumab treatment. In addition, we concluded that among patients who had pre-treatment IL-6 levels lower than 143.12 pg/mL, the probability of clinical improvement after tocilizumab therapy increased from 74.44% to 87.23%. If a patient has a pre-treatment IL-6 level higher than 143.12 pg/mL, the probability of mortality increases from 25.56% to 59% (i.e., pretest odds=0.34; posttest odds=1.45; posttest probability=0.59).

PNI has been suggested as a biomarker for assessing the nutritional and immunological status of patients with chronic disease (27). It is calculated using commonly used parameters, including serum lymphocyte count and albumin level (17). Reduced serum lymphocyte count and hypoalbuminemia are predictors of severe disease and poor outcomes in COVID-19 patients (28,29). In addition, lower PNI may serve as a predictor of prognosis in COVID-19 patients (30). Among patients who had pre-treatment PNI levels higher than 31.35, the probability of clinical improvement after tocilizumab therapy was 84.27% (i.e., pretest odds=2.85; posttest odds=5.36; posttest probability=0.84). For the first time in the available literature, we now provide cutoffs of PNI level for predicting response to tocilizumab treatment.

SII can be easily calculated from hemogram parameters (18). Fois et al. (14) reported that SII was an independent predictor of hospital mortality in COVID-19 patients. In their study, patients with higher SII values had lower PaO_2/FiO_2 ratios and higher chest CT severity scores, but there were no differences regarding the comorbidities. They suggested that the SII level would be specifically affected by lung injury occurring in COVID-19 patients, rather than an overall deterioration in their clinical status due to comorbidities (14). Similarly, Muhammad et al. (13) revealed that SII had high sensitivity and specificity in predicting the clinical course of COVID-19 patients. In line with those recently published studies, in our study, patients who did not improve after tocilizumab therapy had significantly higher SII levels than those who improved. If a patient had a pre-treatment SII level <3895.92, the probability of clinical improvement was raised to 83.06% (i.e., pretest odds=2.85; posttest odds=4.90; posttest probability=0.83). For the first time in the available literature, we now provide cutoffs of SII level for predicting response to tocilizumab treatment.

CAR, which reflects both the inflammatory state and nutritional status, can be obtained with easily accessible parameters, including CRP and albumin (19). It has been reported that the CAR level could be used as a prognostic indicator of disease severity and has predictive value for in-hospital mortality in COVID-19 patients (15,31). In our study, patients who improved after tocilizumab therapy had significantly lower CAR than patients who did not improve. Also, a pre-treatment CAR level <61.15 raised the probability of treatment being effective to 83.46% (i.e., pretest odds=2.85; posttest odds=5.05; posttest probability=0.83). For the first time in the available literature, we now provide cutoffs of CAR levels for predicting response to tocilizumab treatment.

LDH is an enzyme in nearly all cells throughout the body. Elevated LDH levels were associated with an increased risk of severe disease and mortality in COVID-19 patients (32,33). Decreased oxygenation, multiple organ injury, and a hypercoagulable state can contribute to the elevation of LDH in COVID-19 patients (32). In our study, COVID-19 patients who improved after tocilizumab administration had lower LDH levels than those who did not. The probability of clinical improvement was increased to 88.54% in patients with pretreatment LDH levels lower than 460 U/L (i.e., pretest odds=2.85; posttest odds=7.72; posttest probability=0.88). Similar to our study, Li et al. (26) reported that patients who died after tocilizumab therapy had significantly higher LDH levels at baseline than those with clinically improved levels. In addition, they showed that, while there was no significant improvement in the post-treatment LDH value of patients who died, LDH levels were significantly decreased in the improved group. However, the performance of LDH in predicting treatment response was not evaluated in that study. For the first time in the available literature, we now provide cutoffs of LDH levels for predicting response to tocilizumab treatment.

Study Limitations

The retrospective design of this study and the lack of a control group are the major limitations. In addition, the data were obtained from a single center through the hospital's

electronic database; therefore, patient selection bias could not be completely eliminated. Because the utility of pre-treatment biomarker levels in predicting tocilizumab response was evaluated, post-treatment changes in these biomarker levels were not evaluated.

Because there is an ongoing debate about the role of tocilizumab in treating patients with COVID-19, the drug may have a substantial benefit in certain populations. It is well known that most patients experience only mild to moderate symptoms during COVID-19, and these patients do not require anti-cytokine therapy. However, mortality occurs in a subset of patients who progress to severe and critically ill and may require anti-cytokine therapy, but the efforts for suppression of inflammation do not necessarily reduce mortality in all cases, especially when the inflammation cascade is excessive and therapy is delayed. Moreover, early use of anti-cytokine therapy may lead to both increased costs and risks, including iatrogenic immunosuppression. From this viewpoint, one can claim that there can be a "window of opportunity" for treating COVID-19. To specify this time interval and the patients who will benefit from anti-cytokine therapy, several biomarkers, including those in our results, can be a reference for future research.

Conclusion

In conclusion, the current study showed that hospitalized COVID-19 patients with lower IL-6, LDH, SII, CAR, and higher PNI levels improved after tocilizumab therapy. Although questions about whether the optimal timing of tocilizumab therapy for COVID-19 therapy can be guided by biomarkers remain unanswered, we proposed some parameters that can be easily obtained or calculated. Further prospective studies in different ethnicities are required to confirm our findings.

Ethics

Ethics Committee Approval: The study protocol was first registered in the data of the Turkish Republic Ministry of Health Scientific Research Committee and then approved by the Committee on the Human Research Ethics of the University of Health Sciences Türkiye, Gülhane Faculty of Medicine (date: 26.05.2021, number: 2021/35).

Informed Consent: This was a retrospective cohort study.

Authorship Contributions

Surgical and Medical Practices: M.N.K., Concept: D.T., Design: D.T., M.Ç., F.B., Data Collection or Processing: M.N.K., F.B., Analysis or Interpretation: D.T., E.T., S.Y., Literature Search: D.T., Writing: D.T., M.Ç., S.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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