

Evaluation of Laboratory Parameters and Their Correlation with Covid-19 Severity

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ABSTRACT

Background: Role of laboratory parameters in prediction of COVID-19 severity and the need for ICU admission is not well established and needs further investigations.

Objective: This study aimed to evaluate the role of different laboratory parameters, as a minimally invasive method, in prediction of COVID-19 severity and the need for ICU admission.

Patients and methods: Two hundred COVID-19 confirmed patients were admitted to Zagazig University Isolation Hospitals. They were divided into 2 groups according to disease severity. Group I included 100 patients admitted to ICU with severe COVID-19 infection and group II that included 100 patients with mild to moderate COVID-19 infection.

Results: There was a statistical significance increase in WBCs, PNL and neutrophil/lymphocyte ratio and decrease in lymphocyte among severe cases compared to mild cases. WBCs, lymphocyte, PNL, neutrophil/lymphocyte ratio, urea, d-dimer, LDH, ferritin and CRP had significant validity in prediction of severe cases with accuracy of 63%, 65%, 66%, 70%, 68%, 66%, 65%, 66.5% and 64.5% respectively. WBCs, lymphocyte, PNL, neutrophil/lymphocyte ratio, urea, d-dimer, LDH, ferritin and CRP had significant validity in prediction of mortality among the studied cases with accuracy of 55.5%, 55.5%, 63%, 64.5%, 63.5%, 57.5%, 56.5%, 65% and 62% respectively.

Conclusion: The studied biomarkers can be used as an important assistant in clinical practice at ICU admission to improve prognosis, guide treatment and minimize the mortality rates.

Keywords: Covid-19 severity, Laboratory parameters.

Introduction:

COVID-19 spreads mostly through the airways, primarily via the lungs. Respiratory droplets or aerosols, which include virus-containing particles breathed by a person who is infected, can infect others who are in close touch with the person ⁽¹⁾. A mixture of cell-mediated and antibody-mediated immunity is involved in the human response to COV-19 ⁽²⁾. COVID-19's severity can range from mild to severe. The illness may progress slowly with few or no symptoms, much like the common cold or other upper respiratory illnesses. Some studies estimate that 10% to 20% of COVID-19 patients would develop symptoms lasting longer than a month ⁽³⁾. Septic shock and mortality may result from complications such as pneumonia and acute respiratory distress syndrome (ARDS)⁽⁴⁾. Several studies attempted to use clinical evaluation and laboratory tests to predict severity and ICU admission in COVID-19 patients at the time of initial presentation. According to a study conducted in Wuhan, neutrophilia and an elevated d-dimer level are both risk factors for ARDS and death ⁽⁵⁾. **Liang et al.** ⁽⁶⁾ hypothesized that LDH, direct bilirubin, and the neutrophil to lymphocyte ratio are all indicators of serious disease in COVID-19. As a result, more research is needed on how laboratory measures might help predict COVID-19 severity and the requirement for ICU admission.

We aimed for evaluation of role of different laboratory parameters, as a minimally invasive method, in prediction of COVID-19 severity and the need for ICU admission.

PATIENTS AND METHODS

At Zagazig University Isolation Hospitals, we conducted this case-control on 200 cases with

confirmed COVID-19. They were divided into 2 groups according to disease severity using Egyptian Ministry of Health and Population (MOHP) protocol for diagnosis and treatment of COVID -19 as following: **Group I** included 100 patients admitted to ICU with severe COVID-19 infection, and **group II** that included 100 patients with mild to moderate COVID-19 infection.

Inclusion criteria: COVID-19 confirmed patients (diagnosed by PCR) and admitted to Zagazig University Isolation Hospitals.

Exclusion criteria: Patients < 18 years, patients who were chronically immunosuppressed, pregnant women, patients with malignant disease, patients who were receiving long-term oral corticosteroids or antivirals, and patients had active gastrointestinal nematode infections or allergies

Methods:

Patients' demographics, presenting symptoms and laboratory findings reported at the time of admission, in addition to radiological data and outcome of all enrolled patients positive for COVID-19 infection were obtained as following:

- Full history taking focusing on age, sex, and clinical symptoms with special regard to co-morbidity and drug history.
- Complete medical examination (general, chest, and abdominal examinations).

Severity Assessment:

COVID-19 severity was accessed in the studied patients according to MOHP as follows:

Group (I) involved mild cases when clinical symptoms were minimal without dyspnea or shortness of breath

and normal imaging of chest. Mild cases were indicated for home isolation and close follow up. Moderate cases who showed signs and symptoms of lower respiratory infection and their oxygen saturation (SpO₂) was ≥ 92% on room air at sea level. They were admitted to the isolation hospital.

Group (II) involved severe cases who were defined by any of the following criteria: Respiratory rate > 30 breaths/min, oxygen saturation (SpO₂) was < 92%, PaO₂/FiO₂ < 300 mmHg or more than 50% progression in the chest radiological findings within 24 to 48 hours. Patients with severe cases admitted to intermediate care. Critically illness patients who had respiratory failure, septic shock and/or malty organ dysfunction were admitted to intensive care unit [ICU].

Acute respiratory distress syndrome (ARDS) was diagnosed by the Berlin criteria (7). For the patient's clinical status, Acute Physiology and Chronic Health Evaluation II score (APACHE score) was reported (8).

Nasopharyngeal and oropharyngeal swabs were collected for COVID-19 (PCR) test by using Rotor Gene real-time PCR with fluorescence system (QIAGEN, GmbH, Germany) (9).

- **Radiological investigations:** CT test was used as screening tests for COVID 19 pneumonia. Chest X-ray & echocardiography were performed if needed

Outcome: Clinically, patients of group (I) were considered of good prognosis and the other group (II) were considered of poor prognosis.

Primary outcome: ICU Mortality or comorbidity discharge

Secondary outcomes: Length of stay in ICU

Follow up: Cases were followed up from the time of admission to hospital until discharge or death.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS version 25 was used to analyze the data. The Shapiro Walk test was used to determine if the data were normal. There were two methods used to determine the difference between qualitative variables: Chi square (χ²) and Fisher exact. ANOVA F-test was used to compare quantitative variables across many groups. Kruskal Wallis and Mann-Whitney tests were used. Pairwise comparisons were used to assess numerous population means in pairs to see if they are significantly different from one another. P value ≤ 0.05 was considered significant.

RESULTS:

There were no statistical significance differences found between the studied groups in sex but there was a statistical significance increase in mean age and non-medical occupation among sever cases compared to mild cases (**Table 1**). A statistical significant increase was found in frequency of hypoxia, sepsis, venous thrombosis, shock, DCL, ICU admission and other complications among sever cases compared to mild cases (**Table 2**). In 1st laboratory tests done, a statistical significance increase was found in WBCs, PNL, Neutrophil/lymphocyte ratio, d-dimer, urea, ferritin, LDH and CRP and there was a decrease in lymphocyte among sever cases compared to mild cases (**Table 3**). In 2nd laboratory tests done, a statistical significance increase was found in WBCs, PNL and neutrophil/lymphocyte ratio and there was a decrease in lymphocyte among sever cases compared to mild cases (**Table 4**). Concerning validity of first laboratory results in prediction of sever cases among the studied groups, WBCs, lymphocyte, PNL, neutrophil/lymphocyte ratio, urea, d-dimer, LDH, ferritin and CRP had significant validity in prediction of severe cases with accuracy of 63%, 65%, 66%, 70%, 68%, 66%, 65%, 66.5% and 64.5% respectively) as shown in **table (5)**. There was a statistical significance increase in 2nd PNL and neutrophil/lymphocyte ratio and decrease in 2nd lymphocyte among dead cases compared to cured cases (**Table 6**). There was a statistical significance increase in d-dimer, urea, LDH, ferritin, CRP, WBCs, PNL, neutrophil/lymphocyte ratio and decrease in lymphocyte among dead cases compared to cured cases (**Table (7)**).

Table (1): Info on the patients' demographics

Variable		Group I (Mild) (n=100)		Group II (Severe) (n=100)		t	P
Age: (years)	Mean ± Sd	47.97±16.51		62.07±14.17		6.48	<0.001**
	Range	18-93		22-90			
Variable		No	%	No	%	χ ²	P
Sex:	Male	50	50	51	51	0.02	0.89
	Female	50	50	49	49		
Occupation:	Medical	54	54	7	7	52.11	<0.001**
	Non-medical	46	46	93	93		

Table (2): Complications among the studied groups

Complication		Group I (Mild) (n=100)		Group II (Sever) (n=100)		χ^2	P
		No	%	No	%		
Hypoxia:	No	73	72	43	43	17.21	<0.001 **
	Yes	28	28	57	57		
Sepsis:	No	96	96	74	74	18.98	<0.001* *
	Yes	4	4	26	26		
Venous thrombosis:	No	99	100	77	77	22.92	<0.001 **
	Yes	1	0	23	23		
Shock:	No	100	100	83	83	18.58	<0.001 **
	Yes	0	0	17	17		
DCL:	No	100	100	86	86	15.05	<0.001 **
	Yes	0	0	14	14		
Other:	No	100	100	87	87	13.9	<0.001 **
	Yes	0	0	13	13		
	AF			2	2		
	Mucomyosis			6	6		
	Myocarditis			3	3		
	TTP			2	2		
ICU admission:	No	96	73	0	0	184.6	<0.001* *
	Yes	4	27	100	100		

Table (3): First laboratory results among the studied groups

Variable		Group I (Mild) (n=100)	Group II (Sever) (n=100)	Test	P
Hb (gm/dl)	Mean ± Sd	12.53±1.67	12.74±1.98	1.23	0.22 NS
Platelets: (x10³/mm³)	Mean ± Sd	185±39.56	209.5±49.6	1.06	0.29 NS
WBC: (x10³/mm³)	Mean ± Sd	7.65±1.23	10.5±1.81	4.23	<0.001**
Lymphocyte: (x10³/mm³)	Mean ± Sd	1.2±0.28	0.9±0.18	4.56	<0.001**
PNL: (x10³/mm³)	Mean ± Sd	5.65±1.82	8.45±1.81	5.31	<0.001**
Neutrophil/lymphocyte	Mean ± Sd	3.9±0.97	9.68±2.31	6.53	<0.001**
INR	Mean ± Sd	1.09±0.23	1.08±0.22	0.02	0.98 NS
D dimer (mcg/ml)	Mean ± Sd	0.79±0.17	1.2±0.15	3.38	0.001**
Urea: (mg/dl)	Mean ± Sd	17.35±3.51	26.5±6.21	4.89	<0.001**
Creatinine: (mg/dl)	Mean ± Sd	0.79±0.13	0.94±0.14	1.72	0.09 NS
ALT: (IU/l)	Mean ± Sd	26.9±5.41	28.3±6.23	0.61	0.54 NS
AST: (IU/l)	Mean ± Sd	28.3±6.91	34±8.71	1.74	0.08 NS
LDH: (U/l)	Mean ± Sd	374.5±9.98	497.5±9.98	2.29	0.02*
S. Ferritin: (mg/l)	Mean ± Sd	420.25±88.63	956.9±91.32	5.25	<0.001**
CRP: (mg/dl)	Mean ± Sd	40.03±3.98	79.9±13.98	3.71	<0.001**

Table (4): Second laboratory results among the studied groups

Variable		Group I (Mild) (n=100)	Group II (Sever) (n=100)	Test	P
Hb (gm/dl)	Mean ± Sd	12.29±1.92	12.37±2.21	0.55	0.58 NS
Platelets: (x10³/mm³)	Mean ± Sd	211.5±50.12	203±45.61	0.65	0.52 NS
WBC: (x10³/mm³)	Mean ± Sd	8.05±1.91	12.05±2.23	5.73	<0.001**
Lymphocyte: (x10³/mm³)	Mean ± Sd	1.4±0.21	1±0.18	3.41	0.001*
PNL: (x10³/mm³)	Mean ± Sd	5.8±1.31	9.9±2.14	6.65	<0.001**
Neutrophil/lymphocyte	Mean ± Sd	4.86±1.17	11.07±2.18	7.11	<0.001**

Table (5): Validity of First laboratory results in prediction of sever cases among the studied groups

Variable	Cut off	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
Hb	>12.35	0.53 (0.41-0.63)	62%	65%	63.9%	63.1%	63.5%	0.45 NS
Platelets	>185	0.54 (0.46-0.62)	62%	50%	55.3%	56.8%	56%	0.29 NS
WBC	>7.65	0.67 (0.60-0.75)	72%	54%	61%	65.8%	63%	<0.001**
Lymphocyte	<1.15	0.69 (0.61-0.76)	70%	60%	63.6%	66.7%	65%	<0.001**
PNL	>6.45	0.72 (0.65-0.84)	72%	60%	64.3%	68.2%	66%	<0.001**
Neutrophil/lymphocyte	>5.66	0.77 (0.70-0.83)	79%	61%	66.9%	74.4%	70%	<0.001**
INR	>1.03	0.52 (0.43-0.60)	56%	54%	54.9%	55.1%	55%	0.70 NS
Urea	>20.45	0.72 (0.65-0.79)	71%	65%	67%	69.1%	68%	<0.001**
Creatinine	>0.89	0.56 (0.48-0.64)	57%	62%	60%	59%	59.5%	0.13 NS
ALT	>21.59	0.56 (0.48-0.64)	69%	46%	56.1%	59.7%	57.5%	0.15 NS
AST	>230.1	0.53 (0.44-0.61)	64%	52%	57.1%	59.1%	58%	0.07 NS
D dimer	>0.55	0.65 (0.57-0.73)	75%	57%	63.6%	69.5%	66%	<0.001**
LDH	>370	0.61 (0.51-0.67)	69%	61%	63.8%	66.3%	65%	0.02*
S. Ferritin	>512.2	0.72 (0.65-0.79)	75%	58%	64.1%	69.9%	66.5%	<0.001**
CRP	>45.6	0.65 (0.57-0.73)	74%	55%	62.2%	67.9%	64.5%	0.002*

Table (6): Relation between laboratory results and mortality among the sever cases group

Variable		Cured (n=46)	Dead (n=54)	Test	P	
1st	INR	Mean ± Sd	1.04±0.17	1.12±0.25	1.91	0.06 NS
	D dimer (mcg/ml)	Mean ± Sd	1(0.4-3.13)	1.4(0.62-3.53)	0.78	0.43 NS
	Urea: (mg/dl)	Mean ± Sd	26.1±6.59	27.25±6.98	1.53	0.13 NS
	Creatinine: (mg/dl)	Mean ± Sd	0.9±0.17	0.98±0.18	0.49	0.62 NS
	ALT: (IU/l)	Mean ± Sd	29.7±6.99	27.8±6.32	0.21	0.84 NS
	AST: (IU/l)	Mean ± Sd	33.75±8.1	34.6±8.15	0.83	0.41 NS
	LDH: (U/l)	Mean ± Sd	394±8.61	526±23.61	1.3	0.19NS
	S. Ferritin: (mg/l)	Mean ± Sd	846±22.31	1082±26.23	1.41	0.16 NS
	CRP: (mg/dl)	Mean ± Sd	66.85±13.68	98.5±16.51	1.53	0.13 NS
	Hb (gm/dl)	Mean ± Sd	12.99±1.89	12.52±2.05	1.18	0.24 NS
	Platelets: (x10 ³ /mm ³)	Mean ± Sd	225±49.63	190±40.39	1.37	0.17 NS
	WBC: (x10 ³ /mm ³)	Mean ± Sd	10.3±2.98	10.6±2.99	0.76	0.45 NS
	Lymphocyte: (x10 ³ /mm ³)	Mean ± Sd	0.9±0.12	1.0±0.19	0.23	0.82 NS
	PNL: (x10 ³ /mm ³)	Mean ± Sd	7.95±1.02	9.35±2.81	0.85	0.40 NS
	Neutrophil/lymphocyte	Mean ± Sd	8.29±1.81	10.06±2.98	0.75	0.45 NS
	Hb (gm/dl)	Mean ± Sd	12.65±1.86	12.13±2.46	1.18	0.24 NS
	Platelets: (x10 ³ /mm ³)	Mean ± Sd	205.5±36.69	203±33.89	0.36	0.72 NS
2nd	WBC: (x10 ³ /mm ³)	Mean ± Sd	11.45±2.11	13.55±3.26	1.72	0.08 NS
	Lymphocyte: (x10 ³ /mm ³)	Mean ± Sd	1.2±0.26	0.9±0.18	1.99	0.04*
	PNL: (x10 ³ /mm ³)	Mean ± Sd	9.3±2.10	12.45±2.14	2.17	0.03*
	Neutrophil/lymphocyte	Mean ± Sd	7.59±1.81	13.5±2.54	3.23	0.001*

Table (7): Relation between laboratory results and mortality among the studied groups

Variable		Cured (n=145)	Dead (n=55)	Test	P	
1st	INR	Mean ± Sd	1.07±0.21	1.12±0.24	1.46	0.15 NS
	D dimer (mcg/ml)	Mean ± Sd	0.8±0.17	1.3±0.21	2.54	0.01*
	Urea: (mg/dl)	Mean ± Sd	20±4.12	27±5.29	3.7	<0.001**
	Creatinine: (mg/dl)	Mean ± Sd	0.81±0.12	0.96±0.13	1.25	0.21 NS
	ALT: (IU/l)	Mean ± Sd	28.3±0.63	28±0.64	0.51	0.61 NS
	AST: (IU/l)	Mean ± Sd	30.2±6.81	35±8.91	1.77	0.08 NS
	LDH: (U/l)	Mean ± Sd	391±9.51	524±12.61	2.43	0.02*
	S. Ferritin: (mg/l)	Mean ± Sd	586±13.25	1123±45.16	4.14	<0.001**
	CRP: (mg/dl)	Mean ± Sd	52.15±11.12	96±23.35	3.2	0.001*
	Hb (gm/dl)	Mean ± Sd	12.67±1.67	12.54±2.04	0.43	0.67 NS
	Platelets: (x10 ³ /mm ³)	Mean ± Sd	198±22.31	190±19.81	0.85	0.40 NS
	WBC: (x10 ³ /mm ³)	Mean ± Sd	8.4±1.9	10.6±2.11	2.85	0.004*
	Lymphocyte: (x10 ³ /mm ³)	Mean ± Sd	1.1±0.14	0.8±0.11	2.6	0.009*
	PNL: (x10 ³ /mm ³)	Mean ± Sd	6.5±1.11	9.3±1.89	3.54	<0.001**
	Neutrophil/lymphocyte	Mean ± Sd	5.6±1.31	9.92±2.13	4.19	<0.001**
2nd	Hb (gm/dl)	Mean ± Sd	12.38±1.89	12.19±2.47	0.60	0.55 NS
	Platelets: (x10 ³ /mm ³)	Mean ± Sd	208±6.81	203±42.95	0.83	0.41 NS
	WBC: (x10 ³ /mm ³)	Mean ± Sd	9±2.15	13.1±3.14	4.53	<0.001**
	Lymphocyte: (x10 ³ /mm ³)	Mean ± Sd	1.3±0.24	0.9±0.11	3.58	<0.001**
	PNL: (x10 ³ /mm ³)	Mean ± Sd	7±1.41	12.4±2.81	5.36	<0.001**
Neutrophil/lymphocyte	Mean ± Sd	5.96±1.12	13.43±2.81	6.48	<0.001**	

DISCUSSION

Decompensated cirrhosis frequently results in spontaneous bacterial peritonitis as a complication. COVID-19, a novel coronavirus that has infected millions of people around the world, has been identified as the cause of SARS. COVID-19 can induce life-threatening acute respiratory distress syndrome and severe pneumonia (10). In order to accurately forecast mortality and administer the correct medication for COVID-19 patients, it is critical to study the changes and influence of routine blood values (RBVs) (11).

In our study, there was a statistical significance increase in mean age that was distributed as 47.97 ± 16.51 and 62.07±14.17 for group I and group II, respectively. Also, a statistical significance increase in non-medical occupation among sever cases (group II) compared to mild cases (group I). These results agree with Wang *et al.* (12) who reported that the median age was 56 years (interquartile range, 42-68; range, 22-92 years) and that 75 (54.3%) were men. Additionally, our study is in agreement with Basheer *et al.* (13) who reported that COVID-19 disease was found to be more severe as the patient's age increased. Our study's survivors were younger and more likely to be overweight males than the non-survivors.

Regarding first and second laboratory data among our studied groups, there was a statistical significance increase in WBCs, PNL, neutrophil/lymphocyte ratio, d-dimer, urea, ferritin, LDH and CRP and decrease in lymphocyte among sever cases (group II) compared to mild cases (group I). Our study revealed a statistical significance increase in 2nd PNL and neutrophil/lymphocyte ratio and decrease in 2nd lymphocyte among cured cases compared to dead cases. There was a statistical significance increase in d-dimer, urea, LDH, ferritin, CRP, WBCs, PNL,

neutrophil/lymphocyte ratio and decrease in lymphocyte among dead cases compared to cured cases. Our results agree with Qin *et al.* (14) where they discovered a number of changes in WBCs between COVID-19 patients with and without severe disease. Both groups showed a rise in leucocytes, but the severe group showed much larger increase than the other groups. (5.6 vs 4.9 × 10⁹ /L; P < 0.001) for case, having an elevated ratio of neutrophils to lymphocytes (NLR) (5.5 vs 3.2; P < 0.001). Also, Cheng *et al.* (15) reported depleted lymphocyte levels in the majority of severe cases of COVID-19 patients.

A rise in the level of d-dimer indicates the activation of coagulation and fibrinolysis, which are caused by the lysis of cross-linked fibrin (16). Our results coordinate with Zhang *et al.* (16) who found that d-dimer levels of 2.0 µg/ml or more on admission in severe cases. Moreover, our findings are in agreement with Xiang *et al.* (17) in cases where renal indicators such as serum urea and markers of glomerular filtration rate (GFR) were markedly elevated in severe cases. This could be as a result of serious issues with the coagulation system. Besides, our findings agree with Meschiari *et al.* (18) study who discovered that patients in intensive care units had much higher levels of LDH than those who weren't (248 U/L vs 151 U/L, p=0.002). Also, our findings agree with COVID-19 investigations, which found that severe cases have higher NLR than non-severe cases because of higher neutrophil and lower lymphocyte counts. Because patients with COVID-19 have persistently low lymphocyte counts (LC), it is possible to employ LC on its own as a biomarker. Patients who were treated had a higher rate of lymphopenia than those who died, according to the research (19).

Concerning outcome among our studied groups, there was a statistical difference regarding severe cases

(group II) compared to mild cases (group I). Our study showed that WBCs, lymphocyte, PNL, neutrophil/lymphocyte ratio, urea, d-dimer, LDH, ferritin and CRP had significant validity in prediction of severe cases with accuracy of 63%, 65%, 66%, 70%, 68%, 66%, 65%, 66.5% and 64.5% respectively. WBCs, lymphocyte, PNL, neutrophil/lymphocyte ratio, urea, d-dimer, LDH, ferritin and CRP had significant validity in prediction of mortality among the studied cases with accuracy of 55.5%, 55.5%, 63%, 64.5%, 63.5%, 57.5%, 56.5%, 65% and 62% respectively). A study of **Guan *et al.*** ⁽²⁰⁾ involved 1099 patients reported supporting evidence correlating extent of tissue damage and inflammation with increasing levels of LDH. Also, **Luo *et al.*** ⁽²¹⁾ reported high levels of LDH continued in the ICU patients post-admission (218 U/l). However, this study may be prone to selection bias, which could potentially reduce its validity. Also **Tan *et al.*** ⁽¹⁹⁾ found performance of CRP is reflected in the area under curve in the receiver operating analysis of 0.87 (95% CI, 0.10–1.00) where values of 83% and 91% represent sensitivity and specificity, respectively. Our findings agree with **Zhang *et al.*** ⁽¹⁶⁾ where an increase in mortality among COVID-19 patients was shown to be associated with blood d-dimer levels more than one microgram per milliliter. COVID-19 in-hospital mortality can be predicted using this method.

In our study the values of validity and accuracy were less than values of a previous studies which was reported during the first and second waves with high mortality. Due to the high death rates of this pandemic, a serious struggle against the disease continues all over the world in the compared previous studies.

CONCLUSION

It is evidenced that the biomarkers levels change according to severity of COVID-19 infection. The studied biomarkers can be used as an important assistant in clinical practice at ICU admission to improve prognosis, guide treatment and minimize the mortality rates.

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