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EVALUATION OF INFECTION MARKERS IN THE PATIENTS WITH COVID-19 AT TERTIARY CARE INSTITUTE: A PROSPECTIVE STUDY

Biochemistry

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ABSTRACT

Objectives: The outbreak of 2019 Novel coronavirus disease (COVID-19) has caused global attention. Due to its rapid spread worldwide, COVID-19 was declared as a public health emergency by the World Health Organization. Although most patients have mild symptoms and good prognosis, severe COVID-19 cases may present with acute respiratory distress syndrome (ARDS) and systemic inflammation. Thus, it is to evaluate the disease severity and investigate possible biomarkers so as to make fast and correct clinical decisions.

Methods: This is a single center, prospective study conducted at Nalanda Medical College and Hospital Patna. We enrolled 100 OPD and in-hospital patients with COVID- 19 admitted to the Nalanda Medical College and Hoapital and analyzed infection biomarkers in covid patients who had been tested for ferritin, PCT, CRP, IL-6 and procalcitonin.

Results: Average level of Ferritin in Covid-19 patients is 18746.34 ng/ml whereas in control patients it is around 226.29 ng/ml. Around 97 percent of patients affected with COVID-19 having Ferritin level very high from the referred range. Average level of D-dimer in Covid patients is 2807.16 ng/ml and in non COVID patients 276.04 ng/ml. All the covid patients have D-dimer level very high than the referred range. Average level of Procalcitonin in Covid and control patients is 0.93 and 0.53 ng/ml respectively. Around three fourth of covid patients and one third of control patients have this level higher than the referred range. CRP level of COVID patients are very high (on an average 483.48 mg/l) in comparison to non covid patients (on an average 6.29 mg/l). All the covid patients have IL-6 level much higher than the referred range.

Conclusion: Our findings suggest that level of Ferritin, D-dimer, PCT, CRP and IL-6 can be used to predict the result of COVID-19 test. They can help in detection of COVID-19 patients.

KEYWORDS

SARS-CoV-2,COVID-19, CRP, D-dimer, ferritin ,IL-6

INTRODUCTION

The ongoing worldwide Coronavirus Disease 2019 (COVID-19) pandemic has posed a huge threat to global public health . The pathogen has been identified as a novel single-stranded ribonucleic acid (RNA) betacoronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. COVID-19 represents a spectrum of clinical severity ranged from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death[2] . Therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality.

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines[3]. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations . Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19[4-6]. Here we performed a prospective study to compare the levels of inflammatory markers between patients with COVID-19 and healthy individuals. Our study will highlight the association of inflammatory markers with the severity of COVID-19 and assist clinicians to investigate possible biomarkers of COVID-19.

MATERIALS AND METHODS

This is a single center, prospective study conducted at Nalanda Medical College and Hospital Patna from February2020 to July2020. We enrolled 100 in-hospital patients(56 males and 44 females) with COVID- 19 admitted to the Nalanda Medical College and Hospital and analyzed infection biomarkers in covid patients who had been tested for ferritin, PCT, CRP, IL-6 and procalcitonin. 100 healthy age matched individuals were considered as control. Control group comprised of 59 males & 41 females.

The study protocol was approved by the Ethics Committee of Nalanda Medical College and Hospital, Patna. A total of 100 patients aged (25-70years) with covid-19 infection satisfying the following inclusion and exclusion criteria were enrolled:

Inclusion Criteria:

Symptomatic patients aged 25-70years with COVID-19 infection coming to Nalanda Medical College& Hospital, Patna whose Real time polymerase chain reaction for SARS-COV-2 are positive.

Exclusion Criteria:

Patients <25years of age were excluded from the study,
Any patient with visible skin infections,
Asymptomatic carriers,
Documented sepsis caused by other pathogens other than SARS-Corv-2.

Serum samples were collected from the patients admitted in Medicine Department, and CRP, PCT, IL-6, D-dimer and ferritin were tested by the clinical biochemistry laboratory. These parameters were measured by spectrophotometry in fully automated clinical chemistry analyzer in Dept of Biochemistry, NMCH Patna. External quality control was done by EQAS and descriptive statistics (mean, standard deviation, percentage) and Student's *t*-test were used. A P-value <0.05 was considered statistically significant.

RESULTS

Ferritin –

Referred range of Ferritin is 30-400 ng/ml. Table 1 below shows that average level of Ferritin in Covid-19 patients is 18746.34 ng/ml whereas in control patients it is around 226.29 ng/ml. Around 97 percent of patients affected with COVID-19 having Ferritin level very high from the referred range. Comparative figure for control patients are only 12 percent. Gender wise there is no significant changes found. It shows that COVID increases the Ferritin level drastically.

Table 1 – Results of FERRITIN

	Case			Control		
FERRITIN	**Less than 30**	**30-400**	**Above 400**	**Less than 30**	**30-400**	**Above 400**
M	0	1.8	98.2	0	88.1	11.9
F	0	4.5	95.5	0	87.8	12.2
Total	0	3.0	97.0	0	88.0	12.0
Mean	18746.34			226.29		

P Values	0.289	0.00
Std. Deviation	175001.30	144.18

Proportions significantly different at 95%

D-DIMER –

Referred range of D-Dimer is less than 400 ng/ml. Study findings reveals (Table 2) that in COVID-19 patients D-Dimer level is increased. Average level of this parameter in Covid patients is 2807.16 ng/ml and in non COVID patients 276.04 ng/ml. All the covid patients have D-dimer level very high than the referred range. Only one fourth of the control patients found to be having D-dimer level slightly high from the referred range. This parameter is also gender neutral.

Table 2 – Results of D-DIMER

	Case		Control	
D-DIMER	**Less than 400**	**Above 400**	**Less than 400**	**Above 400**
M	0.0	100.0	74.6	25.4
F	0.0	100.0	75.6	24.4
Total	0.0	100.0	75.0	25.0
Mean	2807.16		276.04	
P Values	0.000		0.000	
Std. Deviation	2275.94		142.17	

Procalcitonin -

Referred range of Procalcitonin is less than 0.6 ng/ml. Data presented in Table 3 below shows that in case of COVID patients the level this parameter increases in comparison to non-Covid patients. Average level of Procalcitonin in Covid and control patients is 0.93 and 0.53 ng/ml respectively. Around three fourth of covid patients and one third of control patients have this level higher than the referred range.

Table 3 – Results of Procalcitonin

	Case		Control	
Procalcitonin	**Less than 0.6**	**Above 0.6**	**Less than 0.6**	**Above 0.6**
M	21.4	78.6	69.5	30.5
F	25.0	75.0	61.0	39.0
Total	23.0	77.0	66.0	34.0
Mean	0.93		0.53	
P Values	0.000		0.000	
Std. Deviation	0.49		0.27	

Proportions significantly different at 95%

CRP -

Referred range of CRP is less than 6 mg/l. it can be seen from table 4 below that CRP level of COVID patients are very high (on an average 483.48 mg/l) in comparison to non covid patients (on an average 6.29 mg/l). All the covid patients have CRP level much higher than the referred range. Comparative figure for control patients shows that this level is increased in 53% of the cases.

Table 4 – Results of CRP

	Case		Control	
CRP	**Less than 6**	**Above 6**	**Less than 6**	**Above 6**
M	0.0	100.0	50.8	49.2
F	0.0	100.0	41.5	58.5
Total	0.0	100.0	47.0	53.0
Mean	483.48		6.29	
P Values	0.000		0.000	
Std. Deviation	277.21		2.94	

Proportions significantly different at 95%

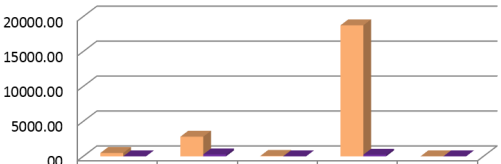
IL-6 -

Referred range of IL-6 is less than 4.40 pg/ml. Table 5 below shows that IL-6 level of COVID patients are very high (on an average 67.95 pg/ml) in comparison to non covid patients (on an average 4.45 pg/ml). All the covid patients have IL-6 level much higher than the referred range. Comparative figure for control patients shows that this level is increased in around one third of the cases.

Table 5 – Results of IL-6

	Case		Control	
IL-6	**Less than 4.40**	**Above 4.40**	**Less than 4.40**	**Above 4.40**
M	0.0	100.0	66.1	33.9
F	0.0	100.0	65.9	34.1
Total	0.0	100.0	66.0	34.0
Mean	67.95		4.45	
P Values	0.001		0.000	
Std. Deviation	96.98		2.18	

Fig 1: Comparison of Inflammatory markers in Covid patients with controls



	CRP	D-DIMER	IL-6	FERRITIN	PCT
Covid patients(Mean)	483.48	2807.2	67.95	18746.3	.9
Controls(Mean)	6.29	276.0	4.45	226.3	.5

DISCUSSION

In this prospective study, we have focused on the infection markers in patients with COVID-19. The serum levels of D-dimer, IL-6, CRP, PCT and ferritin are markedly increased in patients with COVID-19 compared with healthy individuals suggesting that increased D-dimer, IL-6, CRP, PCT and ferritin level might stand for more severe secondary bacterial infection and exacerbated COVID-19[6,7]. The increased levels of inflammatory markers correlate to poor prognosis in COVID-19. In the present analysis, we evaluated serum ferritin levels in COVID-19, which are significantly elevated in covid patients. The function of ferritin is associated with the immune and inflammatory response[8]. When bacterial and/or viral infection takes place, the increase of serum ferritin is related to the release of iron in the reticuloendothelial system, the decrease of the ability of transporting ferritin in liver and spleen, and increased synthesis and release of intracellular ferritin[9-11].

When inflammation or tissue damage happens, CRP can be significantly increased in serum, which is usually used as a unique inflammatory marker in the current clinical practice. PCT is the precursor of calcitonin without hormone activity and is significantly higher in bacterial infection[12,13]. Our study shows that CRP and PCT are markedly increased in COVID-19 patients. The increase of baseline IL-6 level and D-dimer level suggests that it may positively correlate with the severity of COVID-19. One important limitation of the present study is that we have only observed infection biomarkers in limited COVID-19 patients; the small sample size have prevented us from reaching diagnostic value of infection markers in COVID-19 patients.

CONCLUSION

In the present study, we investigated the infection markers in covid patients . Higher levels of CRP, PCT,D-dimer, IL-6 and serum ferritin in COVID-19 patients as compared to healthy individuals might be correlated to secondary bacterial infection, protection from which could be of importance for reducing the mortality rate in COVID-19.

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