Correlation of C-reactive Protein and Lactate Dehydrogenase With The Survival Period in COVID-19 Positive Patients

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Abstract

Background: Ever since the pandemic started, countless people have been affected with the COVID-19 worldwide. In many parts of the world, the number of cases of COVID-19 have declined, but the emerging newer strains are also a cause of concern. During each wave, the severity of the disease has been variable and determination of clinical status has been a challenge in the emergency department.

Aim: To establish relationship between the survival period and oxygen saturation. To establish relationship between the survival period and C-reactive protein (CRP). To establish relationship between survival period and Lactate dehydrogenase (LDH).

Methodology: It is a retrospective observational study of COVID positive patients who died due to the disease at Government Medical College & Hospital, Chandigarh between February 2021 to May 2021. The data was collected from the medical records of the patients who were either laboratory-confirmed by RTPCR or by Rapid Antigen Test. The clinical and the laboratory data was collected and analyzed.

Results: 238 COVID positive patients were included in the study. There was a negative correlation between the survival period and the laboratory biomarkers. It was found that there was no significant correlation between the survival period and the age of the deceased. We found a positive correlation between the survival period and oxygen saturation at arrival in the hospital.

Conclusion: In the present study, it was found that patients with increased values of CRP and LDH had decreased survival period. LDH values were found to be increased in patients who had low oxygen saturation on room air at arrival in the hospital.

Keywords: COVID-19, biomarkers, CRP, LDH, SpO2

Introduction

China reported the first case of Coronavirus disease 2019 (COVID-19) was reported in December 2019, and therefore the primary case was identified within the Wuhan city. The disease has spread worldwide since it began, resulting in an ongoing pandemic. The disease is caused by a novel coronavirus (SARS-CoV-2) (Zhu et al., 2020; Wang et al., 2020) which belongs to lineage B of genus Betacoronavirus(Lu et al., 2020). Many new strains have emerged throughout the world since the outbreak of the disease.

The first case was reported in India on January 30, 2020 and the cases increased by upto 90,000 cases per day. In March 2021, the second wave hit the country by a much more potent delta strain which caused numerous deaths. There was shortage of beds in the hospitals, oxygen cylinders and medical equipments in many parts of the country. Several factors are responsible for the increasing or

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decreasing of COVID 19 cases in different countries. They include the mutations of the coronavirus, following covid appropriate behaviour, effectiveness of the vaccines, vulnerable people as they have not developed immunity.

The incubation period for the disease is 2-14 days (median of 5 days). The symptoms may be mild which include dry cough, fever, fatigue, loss of sense of smell, myalgia to severe progression to acute respiratory distress syndrome (ARDS), multiple organ failure, sepsis and death (Chen et al., 2020; Kluge et al., 2020). The symptoms found in non-severe patients were that of respiratory system infection but in patients with underlying co-morbidities, it led to acute atypical pneumonia and pulmonary damage (Zhu et al., 2020; Wang et al., 2020; Lai et al., 2020). Cardiovascular diseases, hypertension and diabetes mellitus are the common underlying diseases and others were bronchial asthma, tuberculosis, hypothyroidism, cancer and immuno-compromised individuals (Zhou et al., 2020; Alqahtani et al., 2020; Huang et al., 2020).

In severe state of the disease, there is development of hyper inflammatory response that disrupts innate host defense mechanisms, leading to complications like cytokine storm or multiple organ failure (Potempa et al., 2020). Various other studies show that patients admitted to intensive care units had increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF),(Huang et al., 2020), C-reactive protein, interleukin -6, ferritin (Ruan et al., 2020) and biochemical markers like lactate dehydrogenase, where multiorgan damage occurs (Wu & Yang, 2020. There has not been any particular treatment for the disease, therefore, early diagnosis of the disease became an extremely important factor (Gao et al., 2020). The role of laboratory biomarkers plays a key role in early diagnosis and prognosis of the disease. Within present study, we have studied the relationship between the survival period and the biomarkers, CRP and LDH.

CRP increases or decreases in response to inflammation in the body, and the raised levels makes it an important marker in predicting whether the disease is severe or not (Chang et al., 2020). It is synthesized by the liver when there is an infection or inflammation in the body. The normal concentration is less than 10mg/L in blood (Mortensen, 2001). After the onset of the disease, there is rise in serum concentration within 6 to 8 hours and peaks in 48 hours (Chang et al., 2020) and makes it an important marker for viremia. It has a crucial role in activating classical complement cascade of the immune system contributing to proinflammatory cycle (Henry et al., 2020).

Aim of the study

1. To establish the relationship between survival period in COVID-19 positive patients with respect to laboratory biomarkers, CRP and LDH.

2. To establish the relationship between survival period and oxygen saturation at arrival in the hospital.

Methodology

This retrospective observational study was carried out in the patients who died due to the disease at Government Medical College & Hospital, Chandigarh during the period from February 2021 to May 2021. The data was collected from the medical records of the patients, either laboratory-confirmed by RT-PCR or Rapid Antigen Test. The values of laboratory biomarkers, CRP and LDH, oxygen saturation on room air at arrival in the hospital and other parameters were recorded from the medical records of the patients. Analysis of the data was done using the SPSS 26.0 software. Categorical variables are described as frequencies and percentages. Correlations were found using Pearson correlation and relationship was established between the survival period and CRP, LDH and oxygen saturation. P-value of less than 0.05 was considered as statistically significant.

Results

The age group 61-70 years had the maximum number of cases (26.1%) followed by 51-60 years (22.7%). 5.9 % of cases were found in less than 30 years of age. Out of total 238 cases, 134 were males (56.3%) and 104 were females (43.7%). Hypertension (44.5%) was the most common associated comorbidity followed by diabetes mellitus (39.1%). Only 3.8% had history of bronchial asthma and 1.3% had chronic obstructive pulmonary disease. 87.0% of patients had shortness of breath as the presenting

symptom, 68.5% had fever and 40.8% had cough (40.8%) [Table/Fig.1]. Other less common symptoms were altered sensorium (12.2%), chest pain (2.9%).

A total of 80.7% patients required intubation on arrival at the hospital. [Table/Fig. 2] shows the standard deviation and mean for different parameters. Hypertension and bronchial asthma were found to be statistically significant in males and females with p-value < 0.05 [Table/Fig.3]. We found a negative correlation between survival days and the laboratory biomarkers, CRP and LDH [Table/Fig. 4]. We also found a positive correlation between the survival days and oxygen saturation on room air. A negative correlation was found between the oxygen saturation and LDH.

Table/Fig. 2: Showing standard deviation and mean for different parameters

	Mean	Std. Deviation	N
Age	61.51	15.30	238
Survival period	5.76	5.18	238
CRP (mg/ml)	159.32	190.42	238
LDH (IU/L)	1622.82	1387.81	238
SpO2 at arrival (on	74.35	23.83	238

**Table/ Fig. 3: Showing association between comorbidity and sex of an individual**

Comorbidity		Male		Female		Total		p-value
HTN	Yes	49	36.6%	57	54.8%	106	44.5%	0.005**
	No	85	63.4%	47	45.2%	132	55.5%	
DM	Yes	46	34.3%	47	45.2%	93	39.1%	0.088
	No	88	65.7%	57	54.8%	145	60.9%	
BA	Yes	2	1.5%	7	6.7%	9	3.8%	0.036*
	No	132	98.5%	97	93.3%	229	96.2%	
COPD	Yes	3	2.2%	0	0.0%	3	1.3%	0.125
	No	131	97.8%	104	100%	235	98.7%	
Others	Yes	48	35.8%	43	41.3%	91	38.2%	0.384
	No	86	64.2%	61	58.7%	147	61.8%	
	Total	134	100%	104	100%	238	100%	

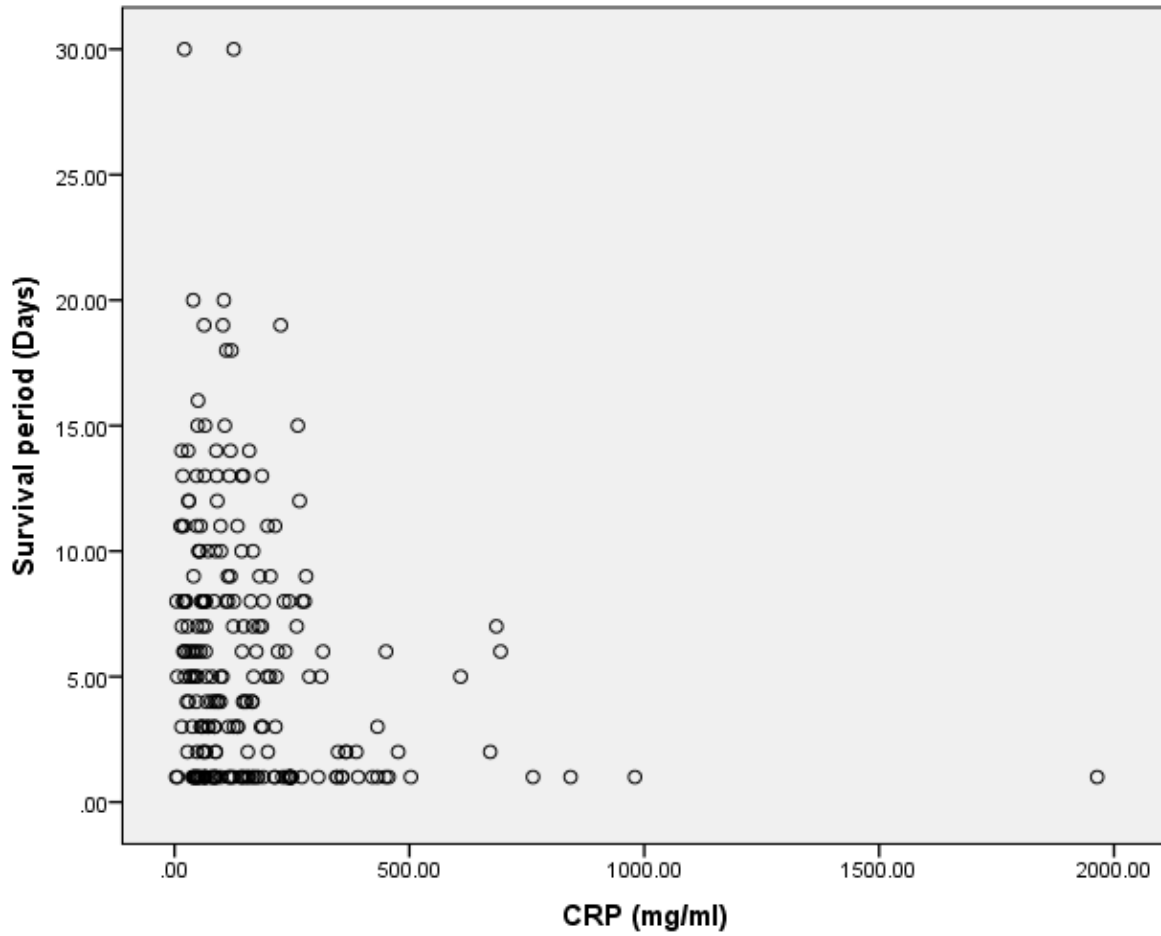**Table/Fig. 4: Showing Pearson correlation between survival period and CRP, LDH and SpO2 at arrival**

		Survival period (days)	CRP (mg/ml)	LDH (IU/L)	SpO2 at arrival (on RA)
	Pearson correlation	1	-.217**	-.182**	.294**
	p-value		.001	.005	.000
	N	238	238	238	238
CRP (mg/ml)	Pearson correlation	-.217**	1	.126	-.105
	p-value	.001		.052	.107
	N	238	238	238	238
LDH (IU/L)	Pearson correlation	-.182**	.126	1	-.295
	p-value	.005	.052		.000
	N	238	238	238	238
SpO2 at arrival	Pearson correlation	.294**	-.105	-.295**	1
	p-value	.000	.107	.000	
	N	238	238	238	238

** Correlation is significant at the 0.01 level (2-tailed)
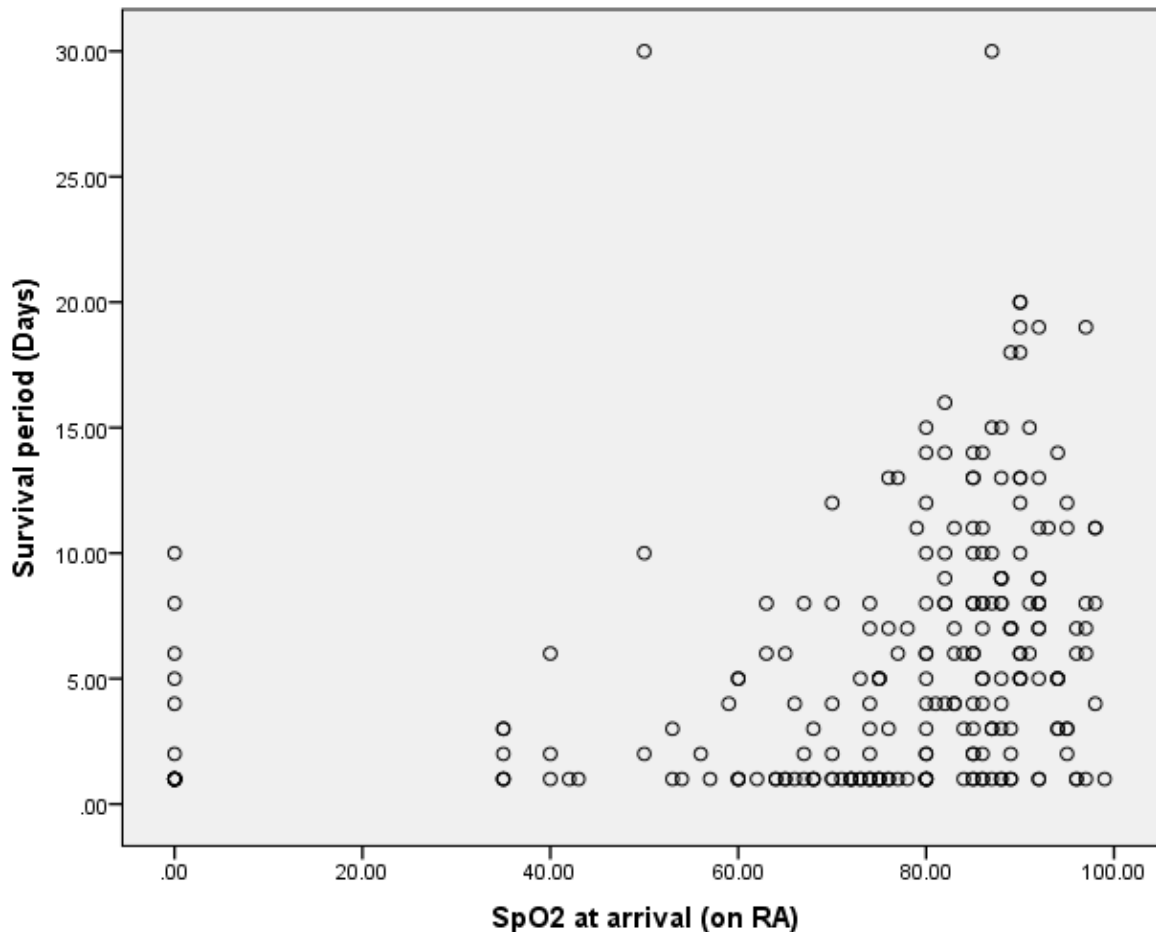
Table/Fig.5: Showing correlation between survival period and LDH
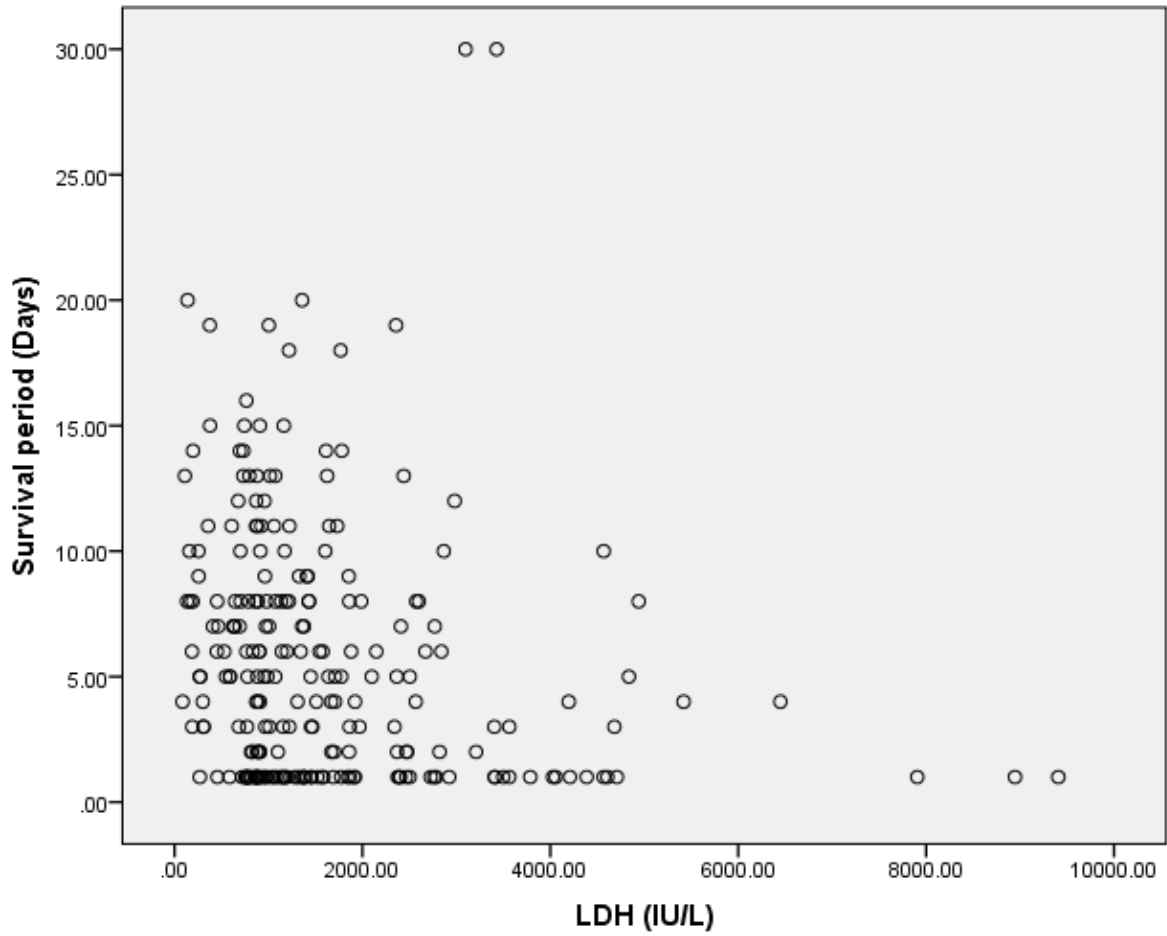
Table/Fig. 6: Showing correlation between survival period and CRP

Table/Fig. 7: Showing correlation between survival period and SpO2

Discussion

In COVID-19 infections, cytokine storm, an acute hyperinflammatory respose, is the major cause of multiple-organ failure. The infection mainly causes pulmonary symptoms but may also lead to multi-organ damage including cardiac muscle, liver and kidneys (Chang et al., 2020). The cytokine storm is reflected by routine laboratory abnormalities (Mortensen, 2001), which consists of an array of increased inflammatory markers, deranged coagulogram and injury indicators which are tissue-specific (Huang et al, 2020). Various markers that are increased during the severe stage of the disease are CRP, LDH, D-dimer, Interleukin-6 (IL-6), ferritin, Procalcitonin (PCT), etc (Henry et al., 2020).

The raised levels of lactate dehydrogenase (LDH), an enzyme that is present in every tissue, have been associated in patients with severe sepsis. Its concentration in the serum above normal levels is an indicator of organ damage. Thus, in patients with severe disease, multi-organ damage occurs and LDH levels are found to be raised above normal (Wu & Yang, 2020). It has been associated with patient mortality, when the levels of LDH do not normalize within 48 hours of sepsis (Zein et al., 2004). Therefore, it has been proposed as an early predictive tool for severe infection (Ferrari et al., 2020).

Numerous studies have been conducted to establish role of biochemical markers in predicting the progression of COVID-19 disease. One study conducted in Italy observed that COVID-19 positive patients showed a significant increase in CRP and LDH values and that these could be used as alternatives to RT-PCR for identifying positive patients (Ferrari et al.,2020). One other study reported that the increased levels of D- dimer, CRP, LDH and ferritin has been associated with poor outcome and mortality (Pan et al., 2020; Liu et al., 2020). Another publication indicated that CRP level was a sensitive and early indicator for COVID-19 on admission (Luo et al., 2020; Wang et al., 2020; Chen

et al., 2020). The findings in our study are consistent with these findings. In the present study, a negative correlation was observed between the survival period and laboratory biomarkers, CRP and LDH and a positive correlation between the survival period and oxygen saturation. Thus, the increased levels of CRP and LDH have been associated with poor outcome, also making them good prognostic factors for predicting the severity of the disease.

Another study conducted in Spain established that LDH can predict early need for invasive ventilation with a sensitivity of 100 percent. The study predicted that there was no requirement of intubation if the LDH levels on admission were <219 U/L (Payán-Pernía et al., 2021). CRP, ferritin and absolute lymphocyte count were also studied alongwith LDH that there was 88 percent probability of early invasive ventilation (Payán-Pernía et al., 2021). The findings in our study were consistent with this study as we found that the survival period was increased in patients who had higher oxygen saturation at arrival to the hospital. We also found that the increased levels of serum LDH had a negative correlation with the survival period, thus making it an important factor in predicting the need for early invasive ventilation.

Limitations of the study

1. Ferritin and other laboratory markers such as IL-6 were not measured as these were not included in the initial laboratory tests.

2. The laboratory parameters were not studied in the patients who survived the disease so that comparison could be made in non-survivors.

Conclusion

In the present study we found that increased serum LDH and CRP were related to a decrease in survival period. In addition, LDH also helped in predicting the need for early intervention. Therefore, CRP and LDH are apt laboratory biomarkers that are helpful in assessing the outcome of the patient at emergency admission to the hospital.

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