

EVALUATION OF THE ROLE OF POTENTIAL BIOCHEMICAL MARKERS TO ASSESS THE SEVERITY OF HOSPITALIZED PATIENTS WITH COVID 19: A TERTIARY HOSPITAL CARE STUDY

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ABSTRACT

INTRODUCTION

Coronavirus disease has become a universal health problem and has resulted in millions of hospitalization and deaths. Coronavirus is a multi-system infection predominantly affecting the respiratory system, resulting in various hematological and biochemical alterations reflected in various investigations. Multitudes of research establishing the role of biomarkers in coronavirus infection are ongoing globally. This study aimed at studying the common biochemical markers like CRP, LDH, and D-dimer to assess the severity of the disease and hospital outcome.

MATERIAL AND METHODS

This was a retrospective cross-sectional study performed at a tertiary care hospital in western Nepal among RT-PCR-positive ICU patients who were ≥ 18 years for a period of six months (May 1 to October 30, 2020). Demographic, clinical, and laboratory data were collected from hospital records and the results were analyzed.

RESULTS

Among 110 admitted patients, 56 were females and 54 were males. The mean age of presentation was 56.5 years. Shortness of breath, cough, and fever were the main presenting complaints. CRP was high in 95% of patients, LDH in 94.5%, and D-dimer in 81.67% of patients. Mechanical ventilation was required in 19.9%, complications were observed in 67.27% and in-hospital mortality was 11.6%. The most common cause of death was acute respiratory distress syndrome.

CONCLUSION

Biomarkers like CRP, LDH, and D-dimer can be used for stratifying coronavirus disease patient's severity and clinical outcome which may later be helpful in identifying risk patients and taking immediate actions in terms of treatment, care, and evaluation.

KEYWORDS

Corona Virus Disease, C - reactive protein, D-dimer, Lactate Dehydrogenase

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by a coronavirus, an RNA virus responsible for an ongoing pandemic that has resulted in over one hundred fifty million cases and more than three million deaths worldwide.¹

The ongoing pandemic of COVID-19 is characterized by respiratory illness and diverse systemic clinical presentations, which in turn are reflected by routine laboratory abnormalities based on the severity of disease presentation.²

Laboratory biomarkers play an essential role in the patient admission protocol, assessment of staging of disease according to severity, prognostication, patient monitoring, and therapeutic guide.³

As of 6 June 2021, more than 173 million cases have been confirmed, with more than 3.72 million confirmed deaths attributed to COVID-19, making it one of the deadliest pandemics in history. COVID-19 biomarkers have been the preferred modality to monitor and predict outcomes and prognosis of the disease.⁴

It is not possible to do all the markers and imaging in every setting because of unavailability and cost-related issues and the clinical characteristics of the patient may vary from place to place. Therefore, we aimed to compare some common laboratory findings and outcomes of illness patterns in our institution so that it would be helpful to find potential prognostic indications contributing to an accurate assessment of the COVID-19 severity.

Various studies have been done regarding biochemical biomarkers and hospital stay outcomes. This study was done to study the common biochemical markers like C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer for assessing the disease severity and outcome of the illness in our clinical setting.

MATERIAL AND METHODS

We had carried out a cross-sectional observational study in patients diagnosed with COVID-19 who were admitted to the intensive care unit of Devdaha Medical College for a period of six months. Devdaha Medical College is a referral site from most of the western part of Nepal and some nearby border areas of India. A wide range of patients from different ethnicity and background visit the institute for treatment and evaluation. COVID-19 was diagnosed with RT-PCR and patients above eighteen years of age were included in the study. Patients with the recent surgical intervention were also excluded. The identification, clinical features, and values of biochemical markers were collected and an outcome study was done in reference to the occurrence of complications, the need for ventilator support, and the results of treatment. The permission for research was taken from the institutional review board and data were collected from records, emergency files, and ward record books in a data collection sheet and analyzed with SPSS software version 19.

RESULTS

A total of 110 patients aged 21- 85 years were included in the study out of which 56 were males and 54 were females (Table 1). The median age of presentation was 50.5 years and most of the patients were above the age of thirty years. A significant number of patients were above 60 years (27.3%).

Table 1. Age categorization of patients

Category	Frequency	Percentage (%)
Below 30	9	8.2
31-45	37	33.6
46-60	34	30.9
Above	30	27.3

Since COVID-19 is an acute respiratory illness, most of the patients have a history of shortness of breath (85.5%) and fever (79.1%) followed by cough, myalgia, loose stool, and loss of taste and smell as given in Table 2.

Table 2. Symptoms

S.N.	Variables	Frequency	Percentage (%)
Symptoms			
1	Shortness of breath	94	85.5
2	Fever	87	79.1
3	Cough	35	31.8
4	Myalgia	16	14.5
5	Chest pain	14	12.7
6	Diarrhea	9	8.2
7	Loss of taste	7	6.4
8	Other	11	10

The frequent co-morbidities reported were hypertension and diabetes. Other comorbidities were cardiac illness and anxiety disorder. Hypothyroidism was present in around 6.3% of patients (Table 3).

Table 3. Comorbid illness with COVID-19

Chronic Disease	Frequency	Percentage (%)
Present	54	49.09
Absent	56	50.90
Chronic Disease	Frequency	Percentage (%)
Hypertension	38	34.5
Diabetes	18	16.4
Cardiac disease	5	4.5
Psychiatric illness	3	2.7
Respiratory disease	4	3.6
Hypothyroidism	7	6.3
Liver disease	2	1.8
Gout	2	1.8
Stroke	1	0.9

Biochemical Markers

We had studied three main biochemical markers (LDH, CRP and D-dimer) in patients and analyzed the occurrence of complications and outcome of hospital stay. LDH (Normal value: 140-280U/L) and CRP levels (Normal value: <10) were high in more than 94% of patients and D-dimer (Normal value: <0.5) was high in 79.08% of patients.⁵

Since COVID-19 is an acute respiratory illness and the study was done in intensive care setting most of the patients

(84.6%) needed supplemental oxygen (FiO₂: 0.6-1). 54.63% of people needed high-flow oxygen out of which half of the patients were managed with a continuous positive airway pressure device (6-10 cm of H₂O) and one-third of patients were managed with mechanical ventilation while a few were managed with oxygen with a face mask and rebreather mask. Other complications were electrolyte abnormality (hypokalemia), GI bleeding, shock, and cardiac arrest as given in table 4. Drug hypersensitivity to remdesivir was observed in one patient.

Table 4. Complications

Complications	No. of cases	Percentage (%)
1 Continuous Positive Airway Pressure	31	28.2
2 High flow of O ₂ (10-15litres/min)	10	19.1
3 Ventilation	21	19.1
4 Acute Respiratory Distress Syndrome	20	18.2
5 Pneumonia	6	5.5
6 Electrolyte abnormality (Hypokalemia)	6	5.5
7 Other	10	9.1

Out of the total patients admitted, more than two-thirds of patients were improved and discharged (Table 5). Thirteen patients expired during the course of treatment and 12 patients were discharged on patient party request and 15 were referred because of unavailability of ventilator or CPAP devices.

Table 5. Outcome of hospital stay

Variable	Frequency	Percentage (%)
Expired	13	11.6
Improved	66	60
LAMA	4	3.6
DOPR	12	10.9
Referred	15	13.6

We had also studied biomarkers in relation to complications and outcomes (Tables 6 and 7). None of the three biomarkers are statistically significant for complications. Only D-dimer was found to be statistically significant for mortality outcome (p -value <0.05) other two were not.

Table 6. Biomarkers versus complications

		Absent	Present	Total	X ² test	p -value
CRP	Less than 10	1	4	5	0.87	0.64
	10-50	14	33	47		
	More than 50	21	37	58		
Total		36	74	110		
LDH	Normal (140-280 U/L)	2	4	6	0.01	0.94
	Increased	34	70	104		
Total		36	74	110		
D-dimer	Less than 0.5	6	21	27	1.9	0.3
	0.5 to 2	17	32	49		
	Mote than 2	13	21	34		
Total		36	74	110		

Table 7. Biomarkers versus mortality

Biomarkers		Outcome No mortality	Mortality	Total	X ² test	P-Value
D-dimer	Less than 0.5	27	0	27	15.342	<0.05
	0.5 to 2	46	3	49		
	More than 2	24	10	34		
Total		97	13	110		
CRP	Less than 10	4	1	5	4.538	0.103
	0-50	45	2	47		
	More than 50	48	10	58		
Total		97	13	110		
LDH	Normal (140-280 U/L)	6	0	6	0.851	0.36
	Increased	91	13	104		
Total		97	13	110		

DISCUSSION

In our study, there is slightly more incidence of COVID-19 in males than females (50.9% vs 40.09%). Adults and elderly population above age forty-five were more affected than young people (64/110). The median age of presentation was 50.5 years indicating that this disease commonly affects the middle-aged and elderly population. This finding was similar to studies done in a tertiary center hospital in Karachi Pakistan and various other studies in different parts of China and India.^{6,7} The high prevalence of disease in the elderly population might be due to low immune status pertaining to chronic illness at this age as in our research the incidence of chronic illness is 46.4%.

Shortness of breath, cough, and fever were the most common clinical manifestations apart from fatigue, myalgia, diarrhea, loss of taste and smell, joint pain, headache, and dizziness. These manifestations were similar to various other studies.^{8,9}

Different biomarkers have been found to be investigated for assessing the prognosis of the patient illness. In our research, we investigated three biochemical markers mainly LDH, CRP and D-dimer.

LDH is one such biomarker of interest since elevated LDH has been associated with worse outcomes in patients with other viral infections in past.¹⁰

In our research, LDH levels were high in 94.5% of patients which was similar to a study done in China.¹¹

The patients with complications had excessively high LDH levels than those without complications which coincide with the study done in china.¹² However, the study was not statistically significant.

This could be explained by the fact that COVID-19 activates inflammasomes leading to cellular pyroptosis and aggressive symptoms ultimately leading to inadequate tissue perfusion and multiple organ failure which results in extremely high LDH level.¹³

CRP levels are high in patients in COVID 19 and it can be used as a useful marker to estimate the likelihood of progression to a severe clinical condition in COVID-19 patients.¹⁴

In our research, CRP was high in 95% of patients and the mean CRP level was 62.6mg/dl. However, a study done by Chen N et al and Chen T et al had high CRP in about 86% of patients.^{15,16}

High CRP levels were associated with a bad prognosis. Among the patients with CRP levels above 50, 72.02% (31/43) were complicated out of which 7 patients were mechanically ventilated and only one patient survived among those who were ventilated. Among the patients with CRP levels above 100, there were complications in 88.3% (15/17). Mortality was high in patients with high CRP levels (12 patients expired among those with complications. CRP levels were significantly high in our studies than in similar studies done in Wuhan, China.¹⁰

As CRP levels at admission predict the disease course, elevated levels can be a valuable marker for predicting an increased risk of disease progression.¹⁷

In COVID-19, there is an uncontrolled release of pro-inflammatory cytokines leading to upregulation of tissue factor expression on the endothelial cells, resulting in an increased pro-coagulant state.¹⁸ Wang et al postulated about the possible formation of pulmonary microthrombus in patients infected with H1N1 infection and a consequent elevation in D-dimer.¹⁹ In our study, the mean d-dimer level was 1.8 mg/dl, 75.5% of patients had a D-dimer level above 0.5 and 30.9% had a D-dimer level above 2mg/dl.

About 81.67% of patients with D-dimer levels above 0.5mg/dl had complications and around 97.4% of patients with d-dimer levels above 2mg/dl had worse complications. The improvement rate decreased from 45.94% to 25.75% when the D-dimer level rises above 2mg/dl.

A high D-dimer at admission was an independent predictor for mortality in COVID-19 patients from Wuhan. Patients with a D-dimer ≥ 2.0 mg/ml had a much higher mortality incidence than those with levels < 2.0 mg/ml which was similar to our study.²⁰

Mortality was high in patients (28.5%) with d-dimer at admission above 2mg/dl which was lower than a study done by Khatri et al in a medical college of Bhairahawa (67.4%) while a study done in china had lesser mortality of around 9.2%.²¹ However, a study done in a tertiary hospital in Chennai, India showed dimer levels on admission were not found to be a strong predictor of mortality.²²

In COVID-19 hyper coagulation is likely to be found at an early stage and it is closely related to disease progression and clinical outcome.²³ Thus d-dimer levels are useful to detect the hypercoagulable state at early stage so that preventive treatment can be started reducing risk of thromboembolism thereby decreasing morbidity and mortality.

Since, it was a single center study with small participation and evaluation of clinical severity with imaging and other biomarkers were not performed the result cannot be generalized to whole population and a large multi institutional prospective study are needed to validate the results.

CONCLUSION

We had studied three biochemical markers namely CRP, LDH and D-dimer at admission of a diagnosed case of COVID-19. Although only D-dimer was found to be statistically significant for mortality outcome, raised value of these markers were related to worse clinical outcome and complications. So, the early evaluation with low cost easily assessable biomarkers and modification of treatment will correctly predict clinical severity. However, the study of biomarkers at the early admission stage will surely help in risk stratification and allotment of available medical resources to save the life of a patient with COVID-19.

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CONFLICT OF INTEREST

None

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