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Role of D-Dimer and LDH in Assessment of Severity of Covid-19

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Abstract

Background: COVID-19 disease due to coronavirus 2 (SARS-CoV-2) infection has been widely spread in India and worldwide. Laboratory investigation values are mainly attributed to the increased inflammatory biomarkers, tissue injury indicators and coagulation parameters. Hence we aimed to investigate D-Dimer and serum LDH and to correlate them amongst non- ARDS cases and ARDS cases which may help to predict severity and outcome of COVID-19. **Subjects and Methods:** Total number of 100 cases enrolled for the study, admitted on priority basis. Consecutive blood tests that included D-Dimer and serum LDH in the study period were reviewed. Patients diagnosed with SARS-CoV-2 infection, diagnosed by RT-PCR and CORAD scaling, in whom, CBC, platelet count, RFT, LFT, RBS, serum D-Dimer and serum LDH had been analysed at the time of admission were selected. For assessment of severity and behaviour of the factors to be analysed the COVID-19 patients were grouped into Non-ARDS (mild) and ARDS (severely ill) cases, factors analysed in both groups and correlated. **Results:** For Non-ARDS patients, the median age was 48 years and for ARDS patients, 60 years. Out of 42 ARDS cases 28 are diabetic (66.7%) $p<0.001$. Out of 39 ARDS cases 35 had mild to severe dyspnea which accounts for 83.3% with p value <0.001. Lymhocyte count and platelet counts are drastically decreased in ARDS cases (Mean=10; 6-14 $p<0.001$ and Mean=1.6X103cells/cu.mm $p<0.001$ respectively). There is decrease in the. ESR is raised in most of the covid cases, a significant increase in ARDS patients (Mean=36; 31.8-42.3 $p<0.05$). In LFT, Bilirubin levels raised significantly (Mean=1.8 and 0.8 $p<0.001$ respectively) along with SGPT significantly increased (Mean=40.3 $p< 0.001$). In all ARDS cases there is significant increase in D-Dimer and serum LDH values (100% and 97.6%). Also in ARDS cases the association between D-Dimer and serum LDH and correlation between these two factors with routine investigations is stronger. **Conclusion:** In summary, this study showed that D-Dimer and LDH could be identified as powerful predictive factors for early recognition of thrombosis and organ injury and thus can predict the severity of COVID-19. Lymphopenia, Thrombocytopenia, with more prominent laboratory abnormalities may be a potential indicator for diagnosis. Older age, high number of comorbidities were associated with severe patients.

Keywords: Covid-19, SARS-COV-2, Non-ARDS cases, ARDS cases

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Introduction

COVID-19 disease which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), originated from Wuhan province of China has emerged as a global pandemic, infecting most of the countries worldwide. In the month of December 2019, SARS-COV-2 was detected in some patients with viral pneumonia who were associated with the Haunan sea food market in Wuhan. Most of the COVID-19 infections were spread by human to human transmission, including health care workers.[1,2] The virus has spread to different parts of China and at least 26 other countries.[3]

By the end of July 2020, more than sixteen million people were infected by highly contagious COVID-19 infection throughout the world.[4] In India, the virus spread rapidly in the month of July 2020 with 4,96,988 estimated active cases and 33,425 deaths. Due to this contagious virus, Delhi, the national capital and Mumbai, the financial capital in India were accounted for 40% of total deaths.[5] Although death rate is alarmingly increasing in India, the recovery rate continues to be more than active cases.

Based on severity and disease presentation, abnormal values in laboratory investigations have been reflected due to acute to severe respiratory illness and diverse systemic clinical representations of COVID-19. These laboratory investi-

gation values are mainly attributed to the increased inflammatory biomarkers, tissue injury indicators and coagulation parameters. As the people infected with COVID-19 continues to rise in India, routine laboratory investigations with biochemical and coagulation markers like D-Dimer and LDH play an important role in assessment of severity and disease outcome.

D-Dimer present in the fibrins get released into the blood when blood coagulation occurs resulting in release of fibrin in the soluble form. Hence increased level of D-Dimer corresponds to activation of blood coagulation which is an aid for diagnostic and therapeutic interventions. Earlier studies show that infections like influenza are associated with increased D-Dimer levels, due to the activation of coagulation by respiratory viruses.[6] In COVID-19, due to systemic inflammation and cytokine storm, one can expect increase in the D-Dimer levels but it can be very significant as the disease progresses because of internal coagulation. COVID-19 infection with Acute Respiratory Distress Syndrome (ARDS) is almost always associated with disseminated intravascular coagulation (DIC)in which D-Dimer levels were seen to be increased. Evaluation of D-Dimer levels may predict the development of ARDS in COVID-19 patients probably due to micro pulmonary embolism.[7–10]

LDH is a major enzyme in glucose oxidation, which is present in all tissues of the body and catalyses pyruvate to lactate in anaerobic glycolysis. LDH present in the tissue gets released into the blood due to injury to tissue resulting in destruction of the cytoplasmic member of the tissue cells.[11] Previous studies have shown that increased levels of LDH are seen in lung diseases. In the patients who were infected by influenza virus, who suffered from pneumonia, LDH was significantly increased in almost 77.8% cases,[12] in whom LDH was considered as an indicator for lung injury. SARS-COV-2 is shown to bind to the angiotensin converting enzyme 2 (ACE 2) receptors of the lung,[13] which explains lungs are the first organs to be affected in the COVID-19 and it is likely to get increased LDH levels in COVID-19 patients. But when disease progresses to severe ARDS, it may result into multiple organ dysfunction and the cytochrome storm.[2,14] Increased LDH levels not only associated with lung injury, liver or cardiac function but may also be seen in multiorgan injury.

Thus, our objective of this cohort is to explore the D-Dimer and LDH levels with other routine laboratory investigations for rapid predicting the severity and mortality of COVID-19 and put it into practice. Our study would be helpful for setting up prognosis and different treatment modalities for COVID-19 patients depending on the disease outcome.

Subjects and Methods

This retrospective cohort study was performed in 2 private hospitals in Belagavi. These two hospitals were converted entirely as COVID hospitals, dedicated for the treatment of COVID 19 patients. The present data was documented and collected from the medical records to identify patients with laboratory-confirmed COVID-19 infection, as represented by a positive SARS-CoV-2-RT-PCR test and High Resolution (HR) CT CORAD scoring. We performed ongoing retrospective manual data abstraction from the records of 100 patients with COVID-19 who received inpatient care from June 30, 2020 to November15, 2020. Consent is being taken from all hospitalized patients for data collection and presentation.

Inclusion Criteria

Patients with laboratory-confirmed SARS-CoV-2 infection according to World Health Organization guidelines:[15] a positive result of real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab. Assessment of severity based on clinical presentation and CORAD scoring was done and the patients presented were grouped into 3 groups according to severity of the disease.

Exclusion Criteria

Patients presented with secondary infection due to bacteria and/or fungus, or patients' data without laboratory investigations at the time of admission were excluded. Patients without or with negative SARS-CoV-2, RT-PCR test results were also excluded from this study.

Consecutive blood tests that included D-Dimer and LDH in the study period were reviewed. Patients diagnosed with COVID-19 in whom D-Dimer, LDH, CBC, platelet count, RFT, LFT, and RBS had been analysed at the time of admission were selected. D-Dimer was measured by quantitative ELISA assay. Serum LDH was measured using fully automated Chemistry analyser system using spectrophotometric assay.

Total number of 100 cases taken for study. The criteria for admission include positive RT-PCR test for COVID-19 with high grade fever with myalgia, SPo2 on pulse oximeter showing < 90%, Dyspnea on mild exertion and cases referred by Govt. officials from peripheries for isolation. All the cases who were subjected for HRCT- chest were showing CORAD 1-5, and HRCT severity scoring was done accordingly. All these RT-PCR positive cases were grouped into 3 groups.

Group 1 consists of mild fever, myalgia, no dyspnea, spo2> 90%.

2nd group consists of high-grade fever, myalgia, mild dyspnea, spo2< 85-90% requiring oxygen inhalation and CORAD<3. There hospital stay ranged from 7-10 days.

Group 3 consists of severe complications of COVID presenting with grade 4 dyspnea, SpO2<80% and CORAD>3, who

were admitted in ICU.

Group 1 is named as Non-ARDS cases and Group 2 and 3 are named as ARDS cases.

Clinical presentation and laboratory outcome data were extracted from medical records. All patients were evaluated at the time of admission, until discharge from the hospital or death.

Results

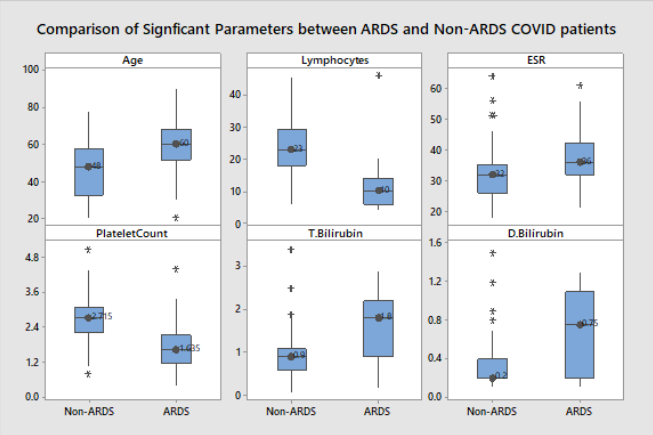
The study population included 100 hospitalized patients with COVID-19, in which 58 cases were Non-ARDS and 42 cases were ARDS. For Non-ARDS patients, the median age was 48 years (IQR 33-58), and 42 (72%) were men. For ARDS patients, the median age was 60 years (IQR 52-69), and 74% were men.

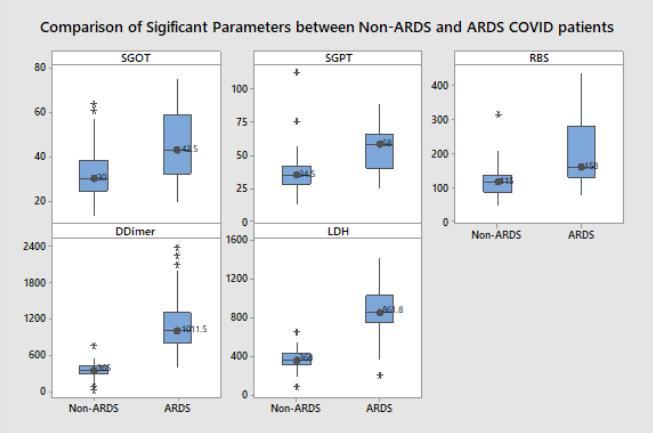
On admission most patients had fever, cough, mild to moderate dyspnea, myalgia, chest discomfort, and fatigue besides, numerous differences in laboratory findings. Compared with Non-ARDS patients, ARDS patients had higher neutrophil counts (N), as well as higher erythrocyte sedimentation rate (ESR), Lymphocytopenia, thrombocytopenia were significant differences in other biomarkers levels as well between two groups, the other notifiables are increase in the Bilirubin and SGPT levels. There is also significant increase in RBS levels suggesting in COVID-19 patients suffering from diabetes chances of ARDS is significant.

The positive association between age and ARDS cases show significant increase in the number of ARDS cases with advanced age. ARDS cases are more between the age groups 40-59 and >60 years as compared to the age group of 20-39. There is total 39 cases of ARDS in >40 years age group to the total 42 ARDS cases. In the later age severity of COVID increased as compared to the earlier age group with probability p<0.001. There is positive association between diabetics and ARDS cases showing diabetics are more prone to get severe COVID infection. Out of 42 ARDS cases 28 are diabetic (66.7%) as compared to 11 cases being diabetic in total 58 Non-ARDS cases (19%) p<0.001. Out of 39 ARDS cases 35 had mild to severe dyspnea which accounts for 83.3% with p value <0.001.

There is significant probability between values of D-Dimer and LDH in ARDS and Non-ARDS cases with p value 0.019 and 0.013 respectively. In all ARDS cases there is significant increase in D-Dimer levels (100%), and LDH levels (97.6%) whereas in Non-ARDS cases these values were raised in 86.2 and 81% respectively.

There is drastic increase in D-Dimer and LDH levels in ARDS cases with significant association with p<0.001. Lymhocyte count is drastically decreased in ARDS cases (Mean=10; 6-14 p<0.001) compared to Non-ARDS cases. ESR is raised in most of the covid cases, a significant increase in ARDS patients (Mean=36; 31.8-42.3 p<0.05). Both these show inflammatory condition in COVID patients. In LFT, T.Bilirubin and D.Bilirubin raised significantly (Mean=1.8 and 0.8 p<0.001 respectively) along with SGPT significantly increased (Mean=40.3 p< 0.001). Also, there is drastic decrease in platelet counts in these ARDS cases (Mean=1.6X10^{3}cells/cu.mm p<0.001) suggesting thrombotic storm in ARDS cases. RBS is significantly raised in ARDS cases proving that uncontrolled/poorly controlled diabetics are more prone to end up with ARDS compared to non-diabetic patients.





In univariate and multivariate analysis of these parameters, all the parameters show significance in univariate analysis p<0.001, while lymphocytes and D-Dimer shows significance in both univariate as well as multivariate analysis showing high sensitivity and specificity, proving them ideal biomarkers for assessment of severity and course of COVID-19 (Table no 3&4).

Table 1: General characteristics of COVID19 patients with and without ARDS

Factors	Categories	ARDS (n=42)	Non-ARDS (n=58)	Total (n=100)	P-value
Sex	Male	31 (73.8%)	42 (72.4%)	73 (73.0%)	0.877
	Female	11 (26.2%)	16 (27.6%)	27 (27.0%)	
Age	20-39	3 (7.1%)	20 (34.5%)	23 (23.0%)	<0.001
	40-59	16 (38.1%)	26 (44.8%)	42 (42.0%)	
	>=60	23 (54.8%)	12 (20.7%)	35 (35.0%)	
Diabetic	No	14 (33.3%)	47 (81.0%)	61 (61.0%)	<0.001
	Yes	28 (66.7%)	11 (19.0%)	39 (39.0%)	
Dyspnea	No	7 (16.7%)	54 (93.1%)	61 (61.0%)	<0.001
	Yes	35 (83.3%)	4 (6.9%)	39 (39.0%)	
D-Dimer	100-250ng/ml	0 (0.0%)	8 (13.8%)	8 (8.0%)	0.019
	>250ng/ml	42 (100.0%)	50 (86.2%)	92 (92.0%)	
LDH	140-280U/L	1 (2.4%)	11 (19.0%)	12 (12.0%)	0.013
	>280U/L	41 (97.6%)	47 (81.0%)	88 (88.0%)	

* P-values based on Chi-square test, Statistically significant P<0.05

Table 2: Comparison of Laboratory Investigations of COVID19 patients with and without ARDS

Parameters	ARDS (n=42)	Non ARDS (58)	Total (n=100)	P-value
Age	60.0 (51.5-67.8)	48.0 (32.5-57.5)	54.0 (40.0-62.8)	<0.001
TC	7800 (5800-12075)	9150 (6800-12850)	8550 (6325-12775)	0.296
Neutrophils	78.0 (68.0-85.0)	71.0 (66.8-82.0)	75.0 (67.0-82.8)	0.164
Lymphocytes	10.0 (6.0-14.0)	23.0 (17.8-29.3)	16.0 (10.0-25.0)	<0.001
HB	12.8 (11.1-13.7)	12.8 (11.6-14.0)	12.8 (11.5-13.9)	0.647
ESR	36.0 (31.8-42.3)	32.0 (26.0-35.3)	32.0 (27.3-40.0)	0.010
Platelet Count	1.6 (1.1-2.1)	2.7 (2.2-3.1)	2.3 (1.6-2.9)	<0.001
Blood Urea	36.0 (25.8-42.0)	30.0 (24.8-36.0)	32.0 (25.0-39.0)	0.072
Creatinine	1.2 (0.9-1.3)	1.1 (0.9-1.2)	1.1 (0.9-1.3)	0.670
T. Protein	6.8 (6.4-6.9)	6.8 (6.6-7.0)	6.8 (6.5-7.0)	0.436
Albumin	3.6 (3.3-3.9)	3.8 (3.5-4.1)	3.8 (3.5-4.0)	0.128
T. Bilirubin	1.8 (0.9-2.2)	0.9 (0.6-1.1)	1.0 (0.8-1.8)	<0.001
D. Bilirubin	0.8 (0.2-1.1)	0.2 (0.2-0.4)	0.3 (0.2-0.8)	<0.001
SGOT	42.5 (31.8-58.8)	30.0 (24.0-38.0)	35.0 (27.0-45.8)	<0.001
SGPT	40.3 (40.3-66.0)	34.5 (28.0-42.0)	38.5 (30.0-57.0)	<0.001
ALP	95.0 (75.0-110.0)	90.5 (76.8-110.0)	92.0 (76.3-110.0)	0.886
RBS	158.0 (129.0-281.0)	115.0 (85.5-135.3)	128.0 (104.0-180.5)	<0.001
D-Dimer ng/l	1011.5 (817.4-1313.3)	365.0 (305.5-432.8)	449.0 (353.8-933.5)	<0.001
LDH U/L	861.8 (753.0-1042.5)	368.0 (311.3-440.0)	465.5 (345.3-827.5)	<0.001

* Data is presented with Median (Interquartile range), P-values based on Mann-Whitney U test, Statistically significant P<0.05

Table 3: Association of laboratory parameters in COVID patients with and without ARDS

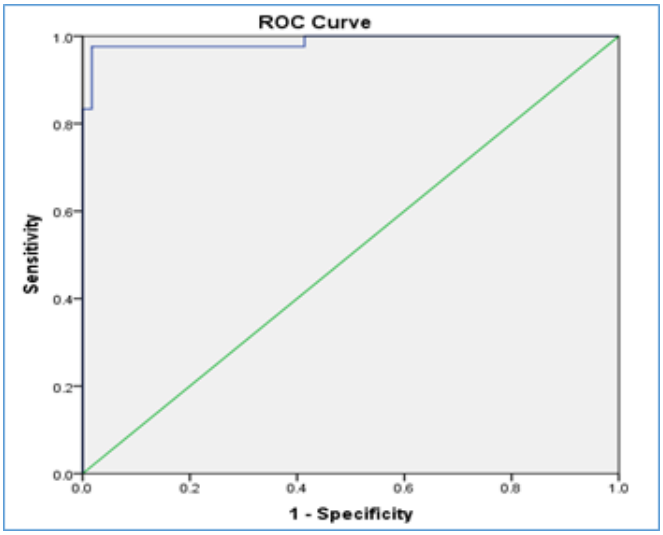
Parameters	Univariate Analysis		Multivariate Analysis	
	P-value	OR (95% CI)	P-value	OR (95% CI)
Age	<0.001	1.06 (1.03-1.09)	-	-
Lymphocytes	<0.001	0.80 (0.74-0.87)	0.027	0.76 (0.60-0.97)
ESR	0.031	1.05 (1.00-1.10)	-	-
PlateletCount	<0.001	0.30 (0.15-0.50)	-	-
T.Bilirubin	<0.001	4.02 (1.96-8.22)	-	-
D.Bilirubin	<0.001	14.2 (3.84-52.73)	-	-
SGOT	<0.001	1.07 (1.03-1.10)	-	-
SGPT	<0.001	1.08 (1.04-1.11)	-	-
RBS	<0.001	1.02 (1.01-1.03)	-	-
D-Dimer ngl	<0.001	1.02 (1.01-1.03)	0.008	1.03 (1.01-1.05)
LDH	<0.001	1.02 (1.01-1.02)	-	-

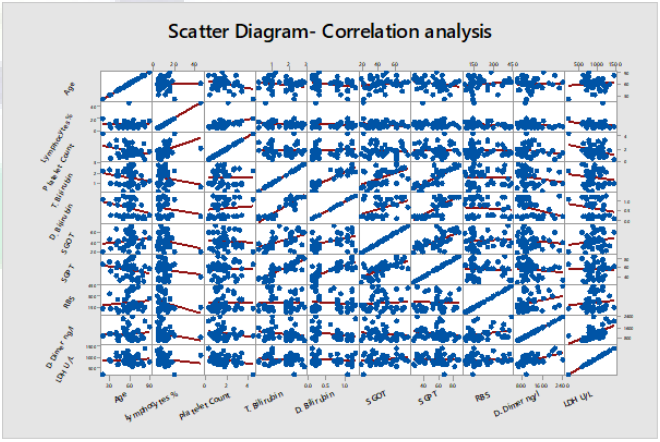
OR: Odds Ratio; CI: Confidence Interval

Table 4: Sensitivity analysis to predict ADRS using D-Dimer levels

Sensitivity	Specificity	AUC	Cut off score
0.98	0.98	0.98	586

ROC analysis showed greater AUC with a value of 98%. It was found that D-Dimer is a best discriminating laboratory parameter to predict patients who will likely to develop ADRS and who will not develop. Cut off score of 586 ngl was established which gave the optimum sensitivity and specificity. It is observed that patients with D-Dimer levels more than 586 ngl will develop at ADRS with a sensitivity of 98% and specificity of 98%.





In correlation analysis, for ARDS patients, there was positive association between D-Dimer and LDH levels at the time of admission (Mean=1011.5; p<0.001 and Mean=861.8; p<0.001 respectively). At the same time, we also analysed the association between these indicators and the values of lymphocyte count, ESR, Bilirubin (Total and direct) levels, SGOT, SGPT and RBS and found that there were great correlations between them in ARDS patients. However, due to the absence of follow-up data, we couldn't study the correlations between biomarkers levels in the course of hospital stay of ARDS patients. But at the time of admission there is significant correlation at 0.05 and 0.01 level as shown in [Table 5]. Thus, there is great correlations with

Table 5: Correlation analysis

Parameters	Age	Lymphoc	ESR	T. Bilirubin	D. Bilirubin	SGOT	SGPT	RBS	D-Dimer ng/l	LDH U/L
Age		-0.256*	0.10	0.05	0.00	0.234*	0.11	0.438**	0.378**	0.407**
Lymphocyt	-0.256*		-0.13	-0.288**	-0.340**	-0.318**	-0.391**	-0.408**	-0.618**	-0.670**
ESR	0.10	-0.13		0.17	0.201*	0.15	0.10	0.17	0.14	0.13
T. Bilirubin	0.05	-0.288**	0.17		0.832**	0.628**	0.707**	0.372**	0.220*	0.289**
D. Bilirubin	0.00	-0.340**	0.201*	0.832**		.493**	0.662**	0.351**	0.225*	0.304**
SGOT	0.234*	-0.318**	0.15	0.628**	.493**		0.703**	0.343**	0.243*	0.398**
SGPT	0.11	-0.391**	0.10	0.707**	0.662**	0.703**		.385**	0.454**	0.501**
RBS	0.438**	-0.408**	0.17	0.372**	0.351**	0.343**	.385**		0.429**	0.499**
D-Dimer ng/l	0.378**	-0.618**	0.14	0.220*	0.225*	0.243*	0.454**	0.429**		0.836**
LDH U/L	0.407**	-0.670**	0.13	0.289**	0.304**	0.398**	0.501**	0.499**	0.836**	

*. Correlation is significant at the 0.05 level; **. Correlation is significant at the 0.01 level

inflammatory cells levels and thrombosis-related factors at the time of admission. Also, patients with comorbidities have shown significant variations in their values compared to the ones without comorbidities.

Discussion

After the COVID-19 epidemic, human corona virus has become one of the main pathogens for respiratory infections. Coronavirus disease has triggered rapidly as worldwide epidemic in less than 3 months leaving many patients suffer from severe pneumonia and resulting in many deaths. This has created an urgency among the researchers worldwide to study on the effective biomarkers which can lead to establish the set of biomarkers to accurately predict the severity of coronavirus disease, thereby guiding clinicians in the clinical management of the patients and the disease outcome.

Our analysis showed that D-Dimer and LDH are raised significantly in ARDS cases as compared to the Non-ARDS cases and act as important predictors in the severity of the disease at the time of admission. Our results are consistent with the findings of review articles that concluded that D-Dimer and LDH, in patients infected with corona virus disease, are a crucial markers for predicting COVID-19 prognosis and mortality in these patients.[16–20]

In addition to the D-Dimer and LDH, the following variables showed significant positive association to the disease severity ($p < 0.01$): Advanced age, Lymphocyte count, Platelet count, ESR, Bilirubin (Total & Direct), SGOT, SGPT and RBS in known Diabetics, which is in accordance with the earlier studies.[21–27] Also in the present study, D-Dimer and LDH levels had particularly strong association with the above mentioned haematological and biochemical variables in ARDS cases. Moreover, in our study it was found that with optimum sensitivity and specificity D-Dimer is a best discriminating laboratory parameter to predict patients who will likely to develop ADRS and who will not develop.

There is development of hypercoagulable state in COVID-19 patients due to endothelial dysfunction, which is induced by infection resulting into decreased fibrinolysis and increased thrombus formation.[28,29] Hypoxia also induces thrombosis in COVID-19 patients by increasing blood viscosity.[30] Because of this early intervention with anticoagulant therapy has been implemented in COVID patients for good results and for better outcome.

In covid-19 patients endothelial dysfunction is mainly limited to lungs as lungs are the first and most commonly affected organs in these patients.[17] D-Dimer, known as indirect marker of thrombus formation, its increase in the COVID-19 patients suggests development of thrombus, particularly

in ARDS patients, indicating poor prognosis. However, as an indirect marker, significant increase in D-Dimer suggested benefit from heparin infusion in a large group of ARDS patients.[17,18]

LDH, an isoenzyme, mainly segregated in liver and heart is also found in almost all human cells. In our study, LDH is positively associated with D-Dimer, SGOT and SGPT which suggests LDH as an isoenzyme of liver and heart. This can be explained by the fact that in COVID-19, heart and liver injury caused by SARS-COV-2 might be due to direct damage to the target organs by virus.[31] In immunosuppressive patients it has been found that LDH is significantly increased which suggests it as not only a metabolic marker but also an immune surveillance prognostic biomarker.[32] There is production of more lactate due to increased LDH, leads to enhancement of immune suppressive cells, including macrophages and dendritic cells and inhibition of cytolytic cells.[33] Due to inflammatory storm that is initiated by SARS-COV-2 elevation of LDH, the immune related factor, could be considered as a predictive factor of poor prognosis in ARDS cases in COVID-19.

Our study has several limitations. This study was conducted single-centered with limited sample size. Furthermore, because follow up study and outcomes were unknown at the time of admission, and we only collected clinical and laboratory data within a week of admission for our analysis. COVID-19 has spread rapidly and has a wide spectrum of severity. A larger cohort study of patients with COVID-19 pneumonia globally would help to further define the clinical characteristics and risk factors of the disease.

Conclusion

In summary, this study showed that D-Dimer and LDH could be identified as powerful predictive factors for early recognition of thrombosis and organ injury and thus can predict the severity of COVID-19. More importantly, lymphocyte counts, ESR, platelet counts, and abnormal liver function and these factors strongly associated with D-Dimer and LDH can be dynamically correlated with the severity of the disease. Hence it is recommended that the D-Dimer and LDH should be used to evaluate the severity and to predict the prognosis and mortality in hospitalized COVID-19 patients. Future clinical studies needed to further clarify the prognostic role in COVID-19, to enhance potential therapeutic value in the inflammation control before end-organ damage.

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