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Original Research Article

D-dimer: a biomarker for predicting disease severity and outcome in hospitalized children with COVID-19 and post COVID multisystem inflammatory syndrome

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ABSTRACT

Background: COVID-19 has presented with varied signs and symptoms with raised inflammatory markers among which D-dimers have been highlighted right from the beginning. Objectives were to analyze the relationship of D-dimers with the disease severity and outcome of children with COVID-19 and MIS-C in a developing country.
Methods: It was a retrospective study conducted at a pediatric tertiary care hospital from March 2020 to November 2021. Clinical and laboratory details of confirmed COVID-19 and post COVID-19 MIS-C cases were recorded. D-dimer testing was performed using Chemiluminescence technique. It's relation with disease severity and predictive role for in-hospital mortality were established by using ROC curves and cut-off values were calculated by using SPSS-24.
Results: Of 272 children, 182 were of COVID-19 and 90 were of MIS-C. The mean age for COVID-19 and MIS-C patients was 5.4±4.8 years and 6.4±3.5 years respectively. Mild disease was seen in 33% cases while 17.6% were critical and 56.2% had some under lying comorbidity at presentation. Mean D-dimers were significantly higher in children with severe disease, who required ICU admission and non-survivors as compared to those with mild or moderate disease, not requiring ICU care and survivors, both in COVID-19 and MIS-C patients. ROC curve identified D-dimer value of ≥4.58 µg/ml (AUC=0.845) for COVID-19 cases and ≥4.73 µg/ml (AUC=0.682) for MIS-C patients as predictive of mortality.
Conclusions: Raised D-dimer level is a reliable predictor of disease severity and outcome in children with COVID-19 and MIS-C. The D-dimer value of 4.58 µg/ml for COVID-19 cases and 4.73µg/ml for MIS-C patients was found to be the cut-off levels for predicting mortality.

Keywords: COVID-19, SARS-CoV-2, D-Dimer, Children, Acute respiratory disease

INTRODUCTION

As COVID-19 pandemic continued, variations in epidemiological and clinical characteristics are documented from different countries around the globe.[1,2] Although severe cases have been reported in literature, it has been found that most infections are not severe in children. In patients with advanced age and particularly those with medical comorbidities, COVID-19 is often severe.[3,4] Few children develop hyperinflammatory shock known as multisystem inflammatory syndrome in children (MIS-C) or atypical Kawasaki like disease syndrome temporarily linked with SARS-CoV-2 which is most commonly reported from Europe and USA but cases from Asia are also documented.[5]

Important diagnostic and prognostic laboratory findings in patient with COVID-19 are leukopenia or leukocytosis,

and lymphopenia, elevated level of lactate dehydrogenase (LDH), serum ferritin and D-dimer levels.[6] Several studies have shown the increased incidence of lymphopenia in patients with serious COVID-19 infection.[7] Hypercoagulability is one of the several features of COVID-19. The cases that will escalate to severe disease and may require intensive care cannot be predicted with any certainty but various hematological markers could help in the optimizing treatment earlier on as well as could provide real-time prognostic information.[8]

Multiple studies have shown that the elevated D-dimer levels are linked with disease severity of community-acquired pneumonia and its clinical outcome.[9] However, D-dimer has not been used in viral pneumonia as a biomarker. D-dimer level is one of the measures used in patients to detect thrombosis. Studies have reported an increase in D-dimer and fibrinogen concentrations in the early stages of COVID-19 disease.[10] There is limited data on the relationship of levels of D-dimers to disease severity and outcome especially in children with MIS-C.

In our study we analyzed the relationship of D-dimers with the disease severity and outcome and tried to establish a cut-off value of D-dimers to predict mortality in hospitalized children with COVID-19 and post COVID-19 MISC.

METHODS

We conducted a retrospective cross-sectional study from March 2020 to November 2021 at the university of the child health sciences, the children's hospital, Lahore, Pakistan.

Patient selection and data collection

Demographic, clinical and laboratory details of all children from birth to sixteen years of age admitted to COVID unit were noted on a pre-designed questionnaire proforma. All patients included who were diagnosed as COVID-19 on the basis of positive nasopharyngeal swab for RT-PCR and post-COVID MIS-C based on positive serology for antibody and presence of clinical criteria according to world health organization (WHO) guidelines.[11] The study was approved by the hospital institutional review board (2021-252-CHICH) and informed consent was taken from the parents/guardians. All suspected cases of COVID-19 who tested negative for RT-PCR and antibody serology, all confirmed children with COVID-19 who did not have D-dimer levels taken, asymptomatic RT-PCR positive children and those with missing clinical details were excluded from the study. The data presented at the ISTH-congress 2021 was a part of continued study and more cases were enrolled according to the inclusion criteria over the extended time period.[12]

Disease severity and outcome

The disease severity was classified using WHO ARI criteria, and a diagnosis of post COVID MIS-C was determined following WHO criteria. The COVID-19 disease was classified as asymptomatic, which means it had no symptoms. Mild: symptoms of the respiratory tract without rapid breathing, Moderate: rapid breathing based on age and pneumonia based on radiological evidence, dyspnea, hypoxia, or >50 percent lung involvement on imaging within 24 to 48 hours indicate Severe illness. ARDS with respiratory failure, shock, or multi-organ dysfunction is a critical disease.[11]

Disease severity of MIS-C was categorized as mild, moderate, severe and critical cases with no asymptomatic type. The previous studies do not show a clear distinction between moderate to severe types. Mild or borderline cases were defined as having fever or dehydration with no hemodynamic instability. Moderate forms meet diagnostic criteria without eligibility for PICU care. While severe and critical cases almost shared same features as respective COVID-19 categories.[13] The outcomes were home isolation, discharged, death, or leaving against medical advice (LAMA).

Laboratory investigations

All patients had laboratory tests done, including a complete blood count with differential count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine transaminase (ALT), ferritin, lactate dehydrogenase (LDH), D-dimer, ECG and a chest X-ray. Children with MIS-C also had echocardiography. Citrated blood samples for D-dimers levels were sent within 12 hours of hospital admission and measured by chemiluminescence technique using MAGLUMI 600 analyzer in Fibrinogen equivalent units (µg/ml). The kits and analyzer remained same during the study and all kits used reference range of <0.5 µg/ml as normal.

Statistical analysis

The data was analyzed using the statistical software SPSS -24. The mean and SD were used to depict quantitative information such as age and D-dimer value. Clinical presentation, disease severity, and outcome were provided as frequency and percentages. We utilized the Chi-square test to determine the significance of the relationship between categorical variables. In order to determine the significance of the difference between two and more than two categories of continuous variables, independent t test and One-way-ANOVA test were used. A $p<0.05$ was considered significant. Receiver operator characteristics (ROC) curve was used to find out how accurately D-dimer levels predict severity and in-hospital mortality. The optimal cut-off value of D-dimers was calculated separately for COVID-19 and MIS-C cases by the curve value nearest to the top-left corner of ROC

graphs. Other measures determined included Area under curve (AUC), sensitivity and specificity.

RESULTS

Our cohort consisted of 272 children with confirmed 182 cases of COVID-19 and 90 cases of MIS-C. Mean age was 5.8±4.4 years (3 months-15 years) and 6.4±3.5 years (5 months-12 years) among COVID-19 and MIS-C patients respectively. Overall male predominance with male-to-female ratio of 2:1. Majority presented with fever 239 (88%), [COVID-19; 158 (86.8%) vs MIS-C; 81 (90%)] followed by cough 159 (58.5%) [COVID-19; 130 (70.4%) vs MIS-C; 29 (32%)]. More children with underlying comorbidities presented with COVID-19 (79%) as compared to MIS-C (5.6%) (Table 1).

Majority cases of COVID-19 were of mild severity (36.2%) while most of MIS-C patients fell in moderate category (41%) at the time of admission. Among the COVID-19 and MIS-C non-survivors 85.2% and 14.8% had an underlying co-morbid condition respectively. The common comorbidities included chronic renal diseases, malignancies, gastrointestinal/hepatic and cardiac disorders. Significantly more patients with elevated D-dimers at presentation had severe or critical disease and required monitoring in high dependency unit or intensive care unit ($p \leq 0.001$). The critical cases of COVID-19 and MIS-C presented with 9.2- and 7.4-times higher D-dimers levels as compared to mild ones respectively. The COVID-19 and MIS-C patients admitted in ICU showed 5.7- and 3.5-fold increase in D-dimers than non-ICU patients. The survivors among COVID-19 cases showed significantly low D-dimers level than deceased (Table 2).

The Table 3 shows that there is significant association between D-dimer rising levels and COVID-19 and MIS-C disease severity as majority of critical cases in both disorders presented with high D-dimers level of more than 10 µg/ml.

The AUC for ROC curve of D-dimer levels at the time of hospital admission for pediatric COVID-19 cases outcome in terms of survival was 0.845 (95% CI 0.875-0.931, $p<0.001$) with sensitivity of 68.2% and specificity of 85.1% (Figure 1). While ROC graph of D-dimer values for MIS-C cases outcome identified AUC of 0.682 (95%CI 0.477-0.557, $p<0.001$) with sensitivity of 65.7% and specificity of 78.5% (Figure 2). From these ROC curves optimal cut-off value of D-dimers was determined to predict in-hospital mortality which found to be 4.58 µg/ml for COVID-19 cases and of 4.73 µg/ml for MIS-C patients.

Based on the cut-off value two groups were analyzed in terms of disease severity. ROC curve analysis for pediatric COVID-19 cases showed AUC of 0.77, sensitivity of 63.75% and specificity of 91.18% to predict severity path. (Figure 3) While ROC graph of MIS-C identified AUC of 0.70, sensitivity of 58.62% and specificity of 81.97% to differentiate severe from non-severe cases (Figure 4).

Table 1: Demographic and clinical characteristics of children admitted in COVID isolation unit (n=272).

Demographic characteristics	COVID-19, n (%)	MIS-C, n (%)
Mean age (years)	5.4±4.8	6.4±3.5
Age groups (years)		
<1	53 (29.1)	6 (6.7)
1-5	42 (23.1)	25 (27.8)
5-10	47 (25.8)	44 (48.8)
10-16	40 (22)	15 (16.7)
Gender		
Male	111 (61)	62 (68.9)
Female	71 (39)	28 (31)
Clinical presentation		
Fever	158 (86.8)	81(90)
Cough	130 (70.4)	29 (32)
Vomiting	46 (25.3)	20 (22.2)
Diarrhea	25 (13.7)	12 (13.3)
Abdominal pain	30 (16.5)	20 (22.2)
Altered sensorium/seizures	19 (10.4)	9 (10)
Body aches	28 (15.6)	14 (15.4)
Respiratory difficulty	103 (56.6)	19 (21.1)
Body rash	10 (5.49)	43(47.7)
Others	32 (17.5)	38 (42.2)
Under lying comorbid condition		
Present	144 (79)	5 (5.6)
No comorbidity	38 (21)	85 (94.4)

Table 2: Disease severity, intensive care and outcome of children in association with mean D-dimers values (µg/ml).

Variables	COVID-19, n=182		P value	MIS-C, n=90		P value
	N (%)	Mean ± SD D-dimers level (µg/ml)		N (%)	Mean ± SD D-dimers level (µg/ml)	
Disease severity						
Mild	66 (36.2)	1.0797±1.5947	<0.001	24 (26.7)	0.9266±1.5904	<0.001
Moderate	36 (19.7)	2.9948±3.22265		37 (41)	3.9026±3.48601	
Severe	38 (20.8)	5.8898±4.19368		23 (25.6)	6.2848±5.8136	
Critical	42 (23)	9.9834±6.60387		6 (6.7)	6.9325±2.6402	
Intensive care						
None	95 (52.1)	1.4144±1.86852	<0.001	46 (51.1)	2.1090±3.1028	<0.001
HDU	42 (23)	3.5930±4.13567		19 (21)	3.6548±3.0401	
ICU	45 (24.7)	8.1894±5.96962		25 (27.7)	7.4790±5.5159	
Outcome						
Home isolation	54 (29.7)	1.6781±2.6532	<0.001		3.3972±3.5446	0.431
Discharged	80 (44)	3.3417±3.70703		77 (85.6)	3.7570±4.4622	
Expired	46 (25.3)	9.6461±6.43483		8 (8.9)	5.8131±3.3078	
LAMA	2 (1)	-		0 (0)	-	

Table 3: Association of COVID-19 and MIS-C disease severity with D-Dimer levels groups.

COVID-19						P value	MIS-C					P value
Disease severity	D-dimers groups (µg/ml)						D-dimers groups (µg/ml)					
	<1	1-5	5-10	>10	Total		<1	1-5	5-10	>10	Total	
Mild	50	14	1	1	66	<0.001	19	4	1	0	24	<0.001
Moderate	11	18	6	1	36		7	20	8	2	37	
Severe	5	15	12	6	38		4	7	9	3	23	
Critical	3	6	14	19	42		0	1	5	0	6	
Total	69	53	33	27	182		30	32	23	5	90	

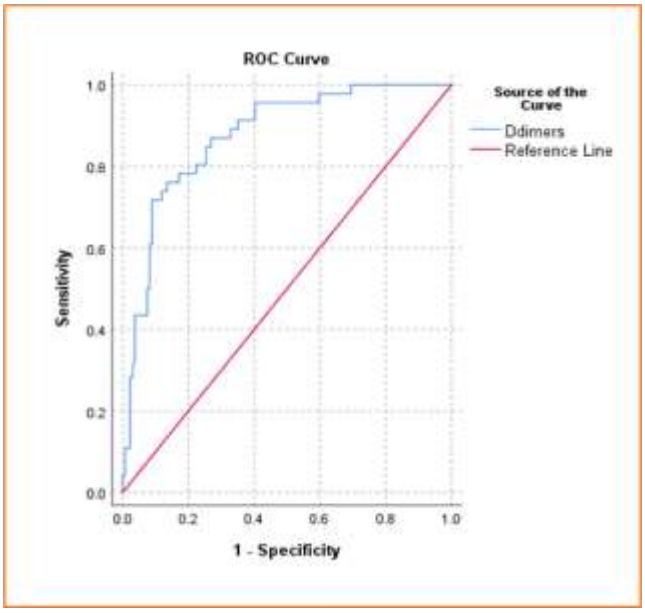

Figure 1: ROC curve for D-Dimer as predictor of in-hospital mortality among COVID-19 hospitalized children. The area under curve (AUC) is 0.845 with 95% CI 0.875-0.931.

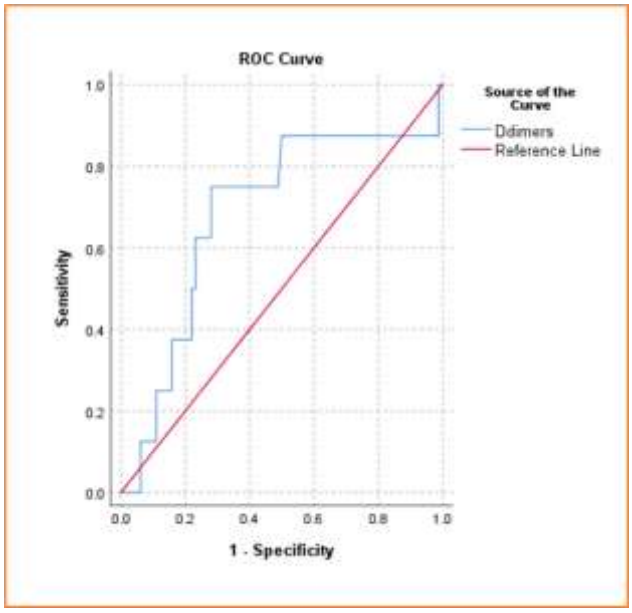

Figure 2: ROC curve for D-Dimer as predictor of in hospital mortality among MISC hospitalized patients. The area under curve is 0.682 with 95% CI 0.477-0.557.

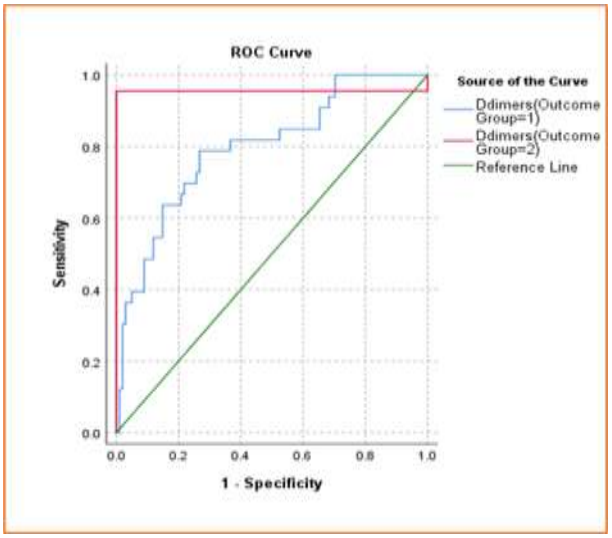

Figure 3: ROC curve to show diagnostic accuracy of D-Dimer to predict severity among COVID-19 hospitalized children.

*(Group 1: Mild/ moderate <5, group 2: Severe/ critical ≥5 µg/ml D-dimer).

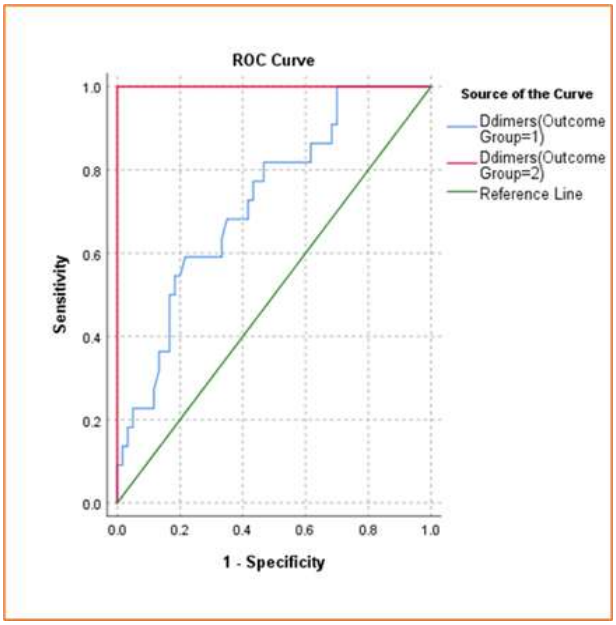

Figure 4: ROC curve to show diagnostic accuracy of D-Dimer to predict severity among MISC hospitalized children.

*(Group 1: Mild/ moderate <5, group 2: severe/ critical ≥5 µg/ml D-dimers).

DISCUSSION

The D-dimer levels are increased in COVID-19 patients and this includes pediatric age group. The effect of these increased levels on survival rates and management strategies makes serial detection of D-dimers levels in COVID-19 important. In the current study we have tried to establish the relationship between D-dimers level, disease severity and mortality in hospitalized patients, not only in COVID-19 but MIS-C patients too. Nature has created a balance in hemostatic system, vascular injury leads to clot formation by intricate work of coagulation factors followed by its breakdown by fibrinolytic system. The D-dimer is formed by degradation of fibrin by the action of plasmin enzyme so this test has been a part of diagnostic algorithm of thrombosis. An interplay between pro-inflammatory cytokines and coagulation system explains D-dimers raise in COVID-19.[14]

In our study, majority of COVID-19 cases presented with mild disease (36.2%) while most of MIS-C patients had moderate to severe disease spectrum. Dong et al reported that 94% of infected children in China were asymptomatic or had mild to moderate disease and less than 1% had critical disease.[15] The difference may be reflected by the fact that majority asymptomatic children did not report to the hospital in our setting. Fever was the most common symptom (88%) found in both groups of patients. However, cough and respiratory difficulty were prominent features of COVID-19 cases while cardiac involvement and body rash were seen in MIS-C cases. Other clinical presentations included vomiting, diarrhea, abdominal pain, altered sensorium/ seizures and body aches. The findings are in concordance to other studies.[4,15,16]

We found that 63.6% of children who presented with COVID-19 and post-COVID MIS-C had raised D-dimer at the time of admission but none experienced thromboembolic event. The reported elevation of D-dimers among infected hospitalized children has been variable ranging between 55.8% and 94.7%.[8,17] Our study has shown that patients with elevated D-dimers at presentation developed severe or critical disease and required monitoring in high dependency or intensive care unit. Patients with higher D-dimers had greater mortality as well. Similar facts are shown by other studies.[9,18,19] However, meta-analysis by Nugroho et al revealed that D-dimer levels of ICU admitted patients were not significantly higher than non-ICU ones.[20] Most of the literature data in this regard is extracted from adult cases of COVID-19. In a study from Wuhan, Yao et al studied COVID-19 admitted patients and reported significantly higher D-dimers in severe ones.[9]

In present study, D-dimers were 9.2 and 7.4 times higher in severe and critical cases of COVID-19 and MIS-C respectively as compared to mild ones. Almost five times D-dimers raise seen in HDU/PICU COVID-19 patients and three times increase in MIS-C cases than non-PICU patients. Non-survivors among both clinical groups showed around nine-fold increase in D-dimers. A four-fold rise in the D-dimer level has been mentioned as a bad prognostic sign.[21] Tang et al and Huang et al reported 3.5-and five-times higher D-dimer levels in COVID-19 patients with severe manifestation respectively.[22,23] Ozen et al found a strong correlation of raised D-dimer levels with severity of COVID-19 pneumonia. They also reported a rising trend in D-dimer levels, with worsening

of clinical and radiological features of patients with COVID-19.[24] Rostami et al has published a comprehensive review showing that overall, more than ten thousand COVID-19 patients have been tested and median D-dimers value reported was 1.53 µg/ml which is close to mild cases in our study.[10]

Multisystem inflammatory syndrome in children (MIS-C) is an inflammatory condition with features of Kawasaki disease and is also considered as a hypercoagulable state. We found significant high D-dimers in severe/critical MIS-C cases as compared to mild/moderate group. However, no difference was found in mean D-dimers values of COVID-19 and MIS-C patients. Al-Ghafry et al has shown that 85% of MIS-C cases had D-dimers >1000 ng/ml with strong correlation to thrombosis tendency. They also reported that D-dimer value more than 2.144 µg/ml had a high sensitivity and specificity to predict ICU admission.[25]

In terms of severity of disease, a cut-off value of 1.5-2 µg/ml has been reported.[26] In our study the cut-off D-dimer value of ≥4.5 µg/ml showed reliability to predict mortality both in COVID-19 or MIS-C diagnosed children. The greater cut-off values in our study may be because of the exclusion of a large number of mild and asymptomatic COVID-19 children. Moreover, in the start of pandemic, not every patient got their D-dimers done. The literature reveals few studies showing relationship of D-dimers level in MIS-C progression.[27,28] Our results suggest that D-dimer levels may contribute in evaluating severity and mortality in COVID-19 and MIS-C pediatric patients. A lot of variations can be seen in the literature in terms of use of different kits, equipment, normal cut-off values and reporting units of D-dimers. These deficiencies have been highlighted by other researchers and the need for standardization is mentioned.

The limitations of the study were that it was a single center, retrospective study with a selection bias as only hospitalized children were studied excluding a large number of asymptomatic ones. Moreover, patients with co-morbid conditions were also included, which could affect D-dimer levels and outcome independently.

D-dimers is a laboratory investigation which is easily available and can guide clinicians for selecting best possible care to patients with COVID-19 or sequalae as a reliable predictor of outcome independent of other parameters. With ever growing challenges in medical field identification of risk factors of severity can undoubtedly prepare us better to combat this or similar diseases in future.

CONCLUSION

Raised D-dimers at the time of hospital admission is a reliable predictive bio-marker for disease severity and in-hospital mortality for both pediatric COVID-19 and MIS-C patients. We found the optimal cut-off D-dimer value of ≥4.58 µg/ml for COVID-19 cases and cut-off D-dimers ≥4.73 µg/ml for MIS-C patients to predict severity of illness and mortality.

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