RELATION OF THREE-TIME POINT ESTIMATION OF INFLAMMATORY MARKERS WITH THE SEVERITY AND OUTCOME IN PATIENTS OF COVID-19 IN A TERTIARY CARE HOSPITAL OF PESHAWAR

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ABSTRACT

Objective: To assess the correlation of different time, point estimations of inflammatory markers of Covid-19 with the severity and outcome of the disease.

Methodology: This study was conducted from December 2021 to May 2022 in the covid-19 ward/ICU of Rehman Medical Institute, Peshawar. A total of 116 adult subjects from both genders were included in study. Three-time point estimation of markers for the assessment of severity and outcome of disease was done. Patients were divided into deceased and recovered categories on outcome and into mild, moderate, severe, and critical categories on disease severity basis.

Results: Three-time point estimation of markers on outcome basis showed that all the markers were significantly higher in deceased subjects as compared to recovered ones. Three-time point estimation according to disease severity revealed that all the markers were higher in critically ill as compared to mildly ill patients. Similarly, majority of the markers were higher in severe as compared to mild, and higher in critical as compared to moderate categories. On ROC curve analysis of markers on admission, only lactate dehydrogenase (LDH) had a good AUC (0.779). On multivariable logistic regression analysis after adjustment for covariates, old age (p=0.001, OR; 2.949), LDH (p=<0.001, OR; 5.995), neutrophil-lymphocyte ratio (NLR), (p=0.029, OR; 2.265), diabetes mellitus (DM) (p=0.001, OR; 2.845) and ischemic heart disease (IHD) (p=0.005, OR; 2.689) predicted the mortality.

Conclusion: LDH, white blood cell (WBC) count, and NLR based on three-time point estimation correlated with morbidity and mortality. Old age, NLR, and LDH on admission, and comorbidities like DM and IHD were significantly associated with mortality.

Keywords: Covid-19; Inflammatory Markers; Ischemic Heart Disease; Diabetes Mellitus; Logistic Regression.

INTRODUCTION

Severe form of covid-19 infection is associated with acute respiratory failure caused by pneumonitis which may require intubation and mechanical ventilation.[1] Associated comorbidities and advanced age are related to a higher magnitude of disease and more adverse outcomes.[2-4] The severe form of the disease is found to be associated with widespread inflammation which can lead to disseminated coagulation, neurological, cardiovascular, and renal disorders, and other end-organ manifestations.[1] It has been established that this widespread inflammation is a sequel to a cytokine release syndrome (CRS) or cytokine storm which is responsible for a higher incidence of morbidity and poor outcomes.[5,6] A lot of cytokines have been thoroughly investigated regarding the cytokine storm, and it has been found that the most important cytokine related to CRS is IL-6. C- reactive protein (CRP), is the end product of IL-6 release and therefore can be predictive of IL-6 production. So, CRP can be used as a marker of ongoing inflammatory process in covid-19 infection.

Disseminated coagulation, which is a common feature of the severe covid-19 disease, is a combination of low-grade disseminated intravascular coagulation and pulmonary thrombotic microangiopathy.[7] Therefore, it is suggested that a coagulation profile comprising D-dimer, platelet count, APTT and fibrinogen should be performed in hospitalized patients.

Different studies have advocated the estimation of serum ferritin as a predictor of adverse outcomes in covid-19 infection. Ferritin is a storage form of iron but

it has been found that macrophages which are important component of any inflammatory response can also produce ferritin.[8] Serum ferritin levels are found to be associated with acute phase response; rather ferritin plays a crucial role in the development of inflammatory response itself.[9] Elevated levels of lactate dehydrogenase (LDH) were reported in patients affected by Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[10] These findings are suggestive of the fact that raised levels of LDH are associated with tissue breakdown in infectious diseases.[11] The LDH is an enzyme which is present in all major organs including lung parenchyma[12], which is a primary site affected by the covid-19 infection.

Several studies have demonstrated that white blood cell (WBC) counts above the normal range are associated with cytokine storm and predict poor outcomes. In addition, it has been proposed that neutrophil-lymphocyte ratio (NLR) also predicts the disease severity at an earlier stage of covid-19 infection.[13]

Few studies are available, which suggest that serial estimation or estimation of inflammatory markers at different time points is correlated in a better way with the disease severity and outcome as compared to their estimation at the time of admission alone.[14] This study therefore, was an attempt to investigate the relation of inflammatory markers measured at different time points with the severity and outcome of covid-19 infection.

METHODOLOGY

A total of 116 patients were selected for this observational cross-sectional study. The study was conducted after approval from the ethical review board of Rehman Medical Institute (RMI) Peshawar. The study was conducted from December 2021 to May 2022. A non-probability consecutive sampling technique was followed. Data from adult symptomatic patients tested positive for RT-PCR (reverse transcription PCR), were collected after informed consent. All the patients were hospitalized in RMI Peshawar. Patients having mild and moderate disease were admitted in covid-19 ward while severe and critical patients were hospitalized in covid-19 ICU. Patients of both genders were included in the study. Those patients were selected for the study whose estimations of high sensitivity C-reactive protein (HS-CRP), D-dimer, Ferritin, LDH and WBC counts at least at three-time points would possibly be done. Patients who lacked relevant clinical data and whose levels of these markers could not be estimated at three-time points, were excluded from the study. RT-PCR was performed in the department of molecular biology of RMI by using CFX96 C 1000 Touch Real-Time PCR Detection System (BIO-RAD). HS-CRP, D-dimer and LDH were measured on Cobas 6000 analyzer series (Roche diagnostics). HS-CRP and D-dimer were measured by using Particle Enhanced Immunoturbidimetric technique while LDH was estimated through a kinetic reaction. Serum Ferritin levels were estimated on Alinity i (Abbott diagnostics) by using the Chemiluminescent Microparticle Immunoassay (CMIA) technique. WBC counts were done by using Sysmex XN-1000 hematology analyzer (Sysmex America, Inc).

Patients were divided into deceased and recovered categories on the outcome basis while based on the severity; patients were split into mild, moderate, severe and critical categories. Categorization of disease severity was based on WHO guidelines for the management of covid-19 infection.[15]

Statistical analysis was done using SPSS (version 23, SPSS IBM Statistics, Armonk, NY, USA) and graphs were made by using GraphPadPrism (version 8, GraphPad Software, La Jolla, CA, USA). The demographic data of scale variables like age and duration of stay were expressed as mean and standard deviation (SD) while categorical variables like gender, age categories and comorbidities were presented as frequencies (n) and percentages (%). The mean age and duration of stay of deceased and recovered categories were compared by independent sample t-test while gender, age categories and comorbidities were compared using the Chi- square test. Values of all the inflammatory markers were subjected to Kolmogorov Smirnov and Shapiro- Wilk tests to assess the distribution of data. Data were not normally distributed. The values of the markers were therefore expressed as medians and interquartile ranges (IQRs). Medians of both, deceased and recovered categories at all three-time points were compared by using the Mann-Whitney U test. A value of <0.05 at 95% confidence interval was considered significant. The three-time points of estimation of different markers were actually, values at admission, peak values during the stay and values before discharge or death. The time point at admission corresponded to day 0 (during 24 hours of admission), the time point of peak value corresponded to day 10 approximately (5-15 days) while the time point before discharge or death corresponded to day 20 approximately (16-25 days). Inflammatory markers measured on admission or day 0 were denoted by suffix 1, those at peak or day 10 by suffix 2 and the ones measured before discharge/death or on day 20 were denoted by suffix 3. Kruskal Wallis test with Bonferoni correction was applied to compare the values of different markers at all three time points in mild, moderate, severe and critical categories. ROC curve was applied to assess the sensitivity, specificity and optimal cut off values of all the markers on admission. The univariate, univariable logistic regression model was applied to evaluate the risk prediction ability of all the inflammatory markers on admission. The markers which significantly predicted mortality on univariable analysis were subjected to univariate, multivariable regression model to assess their risk prediction ability.

RESULTS

Out of 116 patients, 51 died while 65 patients recovered and were discharged. In the mild and moderate categories, there were 28 patients each, while there were 14 patients in the severe category and 46 in the critical category. No patient in the mild and moderate categories died. Most of the patients in critical and severe categories succumbed to death. As shown in Table 1, the mean age of the patients was more in the deceased category (66.75 ± 12.57) as compared to the recovered one (58.28 ± 12.9) and showed a statistically significant difference (p<0.001). There was a statistically significant difference (p-value=0.003) among different age categories in deceased and recovered patients. Gender did not show any significant difference (p-value=0.281) in both the deceased and recovered categories. Duration of hospital stay was significantly (p-value=0.002) greater in deceased patients (13.96 ± 8.98) as compared to recovered ones (10.83 ± 5.46). In the total cohort of subjects, among comorbid conditions, diabetes mellitus had the highest incidence (59.5%) followed by hypertension (51.7%), then ischemic heart disease (25.9%) and then chronic kidney disease (7.8%). The majority of the subjects had more than one comorbid condition. On applying Chi-square test, the incidence of all comorbid conditions was significantly higher in deceased as compared to recovered subjects except chronic kidney disease (CKD) (p=0.503). Table 2 depicts that in deceased subjects, medians and IQRs of HS-CRP (190 ± 320-80), Ferritin (1455 ± 1676-810) and D-dimer (4820 ± 8603-1286) were at their peak on day 10 while those of LDH (792 ± 1101-580), WBC (21.0 ± 28-15) and NLR (27.9 ± 43.9-18) were at their peak on day 20. In recovered subjects, all the markers were at their peak on day 10. The medians of all the markers were compared for both deceased and recovered categories by Mann-Whitney U test. All the values at all-time points were significantly higher in the deceased category.

Figure 1 shows that in deceased patients, LDH, WBC count and NLR were constantly rising at all three-time points, right from the time of admission, while HS-CRP, Ferritin and D-dimer showed a fall after their peak or middle values. In the recovered patients all the markers showed a decline after their middle values.

Figure 2 reveals that the median values of all the markers at all three-time points were higher in critically ill as compared to mildly ill patients. Majority of the markers were higher in severe as compared to mild category. Similarly majority of markers were higher in critical as compared to moderate category. Very few markers showed a significant difference between mild and moderate categories. On the other hand in the critical category, LDH, WBC and NLR showed a constant rise at all three-time points, while HS-CRP, Ferritin and D-dimer showed a decline after their middle or peak values.

On ROC curve analysis, out of all markers on admission, LDH was the only one that had a good AUC (0.779) with a cutoff limit of 312 U/L, a sensitivity of 82.4%, specificity of 51% and a PPV of 78.6%. Table 3 and Figure 3 depict the results of ROC curve analysis.

Logistic regression model for different variables on admission showed that on univariate, univariable regression analysis, all the variables except gender (p=0.282, OR; 0.646), HS-CRP (p=0.098, OR; 0.998), D-dimer (p=0.149, OR; 1.000) and CKD (p=0.50, OR; 1.627) significantly predicted the mortality. On multivariable analysis after adjustment for the covariates, it was found that only age (p=0.001, OR; 2.949), LDH (p; <0.001, OR; 5.995), NLR (p=0.029, OR; 2.265), DM (p=0.001, OR; 2.845) and IHD (p=0.005, OR; 2.689) significantly predicted the mortality, LDH predicting the outcome most of all. LDH had the highest odds of predicting mortality.

DISCUSSION

In this study mean age of the total cohort of subjects was 62 ± 13.39 years. It was more in deceased subjects 66.75 ± 12.57 as compared to recovered ones 58.28 ± 12.9 with a statistically significant difference (<0.001). These findings were comparable to the results drawn by Sharifpour et al.[1] Their study derived a mean cohort age of 63 ± 15 years, a mean age of 71 ± 13 years for non-survivors and 60 ± 15 years for survivors with a p-value of <0.001. Our findings were also consistent with the study conducted by Zhou et al[2] which showed a median cohort age of 56 ± 21 years, 69 ± 13 years of non-survivors and 52 ± 13 years of survivors with a p-value of <0.001. So this study indicates that old age is a risk factor for the covid-19 disease severity, a result augmented by another study conducted by Osibogun et al[16] as well. Osibogun et al concluded that an age of more than 60 years increases the risk of mortality. Our study also concluded that most of the patients who could not survive belonged to 71-90 years age group followed by 51-70 years age category. Our study showed greater chances of mortality in male patients (72.5%) as compared to females (27.4%). This finding was comparable to the results drawn by Zhou et al.[2] According to their study, male non-survivors were 70% as compared to 30% female non-survivors. Similarly Lau et al[17] in their study concluded that the number of males who died was twofold higher than females.

In the present study, duration of hospital stay was significantly higher in subjects who succumbed to death as compared to survivors. Similar results were derived by Zhou et al.[2] Their study showed a median hospital stay of 12.0 (9.0-15.0) days in non survivors as compared to 7.5 (5.0-11.0) days in survivors.

Table 1: Demographics of the total, deceased, and recovered subjects

Demographics	Total (N=116)	Deceased (N=51)	Recovered (N=65)	P-value
Age (Y), Mean ± SD	62 ± 13.39	66.75 ± 12.57	58.28 ± 12.9	<0.001[a]
Age Categories, N (%)				
30 - 50 Y	23 (19.8%)	4 (7.8 %)	19 (29.2%)	0.003[b]
51-70 Y	60 (51.7%)	26 (51%)	34 (52.3%)	
71-90 Y	33 (28.4%)	21 (41.2%)	12 (18.5%)	
Male, N (%)	78 (67.2%)	37/51 (72.5%)	41/65 (63.1%)	0.281[b]
Female, N (%)	38(32.8%)	14/51(27.5%)	24/65 (36.9%)	
Duration of stay (days)	12.21±7.36	13.96±8.98	10.83± 5.46	0.002[a]
Diabetes Mellitus, N (%)	69 (59.5%)	39/51 (76.5%)	30/65 (46.2%)	0.001[b]
Hypertension, N (%)	60 (51.7%)	38/51 (74.5%)	22/65 (33.8%)	<0.001[b]
Ischemic Heart Disease, N (%)	30 (25.9%)	20/51 (39.2%)	10/65 (15.4%)	0.004[b]
Chronic Kidney Disease, N (%)	9 (7.8%)	3/51 (5.9%)	6/65 (9.2%)	0.503[b]

N Number, Y Years, SD Standard deviation, a Independent t-test, b Chi-square test

Table 2: Medians and IQRs of markers at three-time points in recovered and deceased patients

	Deceased		Recovered		
Variables	Median	IQR	Median	IQR	P-value
HS-CRP1	120	254.1-51.4(202.7)	40	231.4-10.4(220.9)	0.003#
HS-CRP 2	190	320-80(240)	58.9	152.4-16(136.4)	<0.001 #
HS-CRP 3	67.6	249.7-12.5(237.2)	10.0	32-3.5(28.4)	<0.001 #
Ferritin 1	1033	1676-443(1233)	529	1527.5-238(1289.5)	0.029 #
Ferritin 2	1455	1676-810(866)	656	1486-311.5(1174.5)	<0.001 #
Ferritin 3	1326	1676-810(866)	469	995.5-309(686.5)	<0.001 #
D-dimer 1	577	1414-256(1158)	355	899-204.5(695)	0.032 #
D-dimer 2	4820	8603-1286(7317)	471	1140-255(885.5)	<0.001 #
D-dimer 3	1981	5713-1044(4669)	353	1006-201(805)	<0.001 #
LDH 1	508	735-359(376)	309	429.5-210(219.5)	<0.001 #
LDH 2	777	1094-506(588)	336	447 -234.5(212.5)	<0.001 #
LDH 3	792	1101-580(521)	290	383.5-215(168.5)	<0.001 #
WBC1	12.0	17-9(8)	10.0	14-6(8.0)	0.007 #
WBC2	19.0	23-15(8)	11.0	17-7.5(9.5)	<0.001 #
WBC3	21.0	28-15(13)	10.0	13-8.0(5.0)	<0.001 #
NLR1	14.1	20.2-7.3(12.9)	6.4	16.9-2.7(14.1)	0.002 #
NLR2	26.0	42.8-15.4(27.4)	10.1	18.7-3.6(15.1)	<0.001 #
NLR3	27.9	43.9-18(25.9)	5.5	15.6-2.6(12.9)	<0.001 #

IQR Inter quartile range, # Mann Whitney U test, Suffix 1 On day 0, Suffix 2 On day 10, Suffix 3 On day 20, HS-CRP High sensitivity C-reactive protein, LDH Lactate dehydrogenase, WBC White blood cells, NLR Neutrophil-lymphocyte ratio

Table 3: AUC and optimal cut-off values of inflammatory markers on admission

Variables	AUC	Optimal cut-off value	Sensitivity	Specificity	PPV	NPV
HS-CRP (mg/L)	0.660	40.05	84.3	53	81.0%	58.1%
Ferritin (µg/L)	0.618	400	80.4	45	74.4%	53.2%
D-dimer (µg/L)	0.617	245	80.4	37	70.6%	50.0%
LDH (U/L)	0.779	312	82.4	51	78.6%	56.8%
WBC (109/L)	0.647	8.5	80.4	44	73.7%	52.6%
NLR	0.671	6.06	84	50	80.0%	56.6%

AUC Area under the curve, PPV Positive predictive value, NPV Negative predictive value, HS-CRP High sensitivity C-reactive protein, LDH Lactate dehydrogenase, WBC White blood cells, NLR Neutrophil-lymphocyte ratio

Table 4: Univariable and Multivariable regression analysis of different parameters on admission

Variable	Univariable			Multivariable		
	p-Value	OR	95% CI	p-Value	OR	95% CI
Age	0.001	2.949	1.919 – 3.979	0.020	2.387	1.793 -- 2.993
Gender	0.282	0.646	0.292 –1.431	-----	-----	-----
Duration of stay	0.030	2.140	1.888 – 3.04	-----	-----	-----
HS-CRP (mg/L)	0.098	0.998	0.995 – 1.000	-----	-----	-----
Ferritin (µg/L)	0.036	2.099	1.799 – 2.900	-----	-----	-----
D-dimer (µg/L)	0.149	1.000	1.000 –1.000	-----	-----	-----
LDH (U/L)	<0.001	5.995	3.993 – 9.997	0.001	4.003	3.094 -- 5.012
WBC (109/L)	0.010	2.013	1.052 – 3.379	-----	-----	-----
NLR (109/L)	0.029	2.265	1.635 – 3.696	0.043	1.055	1.002 -- 1.111
Diabetes mellitus	0.001	2.845	1.875 – 3.586	0.011	2.456	1.985 – 2.995
Hypertension	<0.001	5.021	2.934 – 8.059	-----	-----	-----
Ischemic heart disease	0.005	2.689	1.35 – 3.021	0.022	2.310	1.115 – 2.950
Chronic kidney disease	0.50	1.627	0.387 – 6.849	-----	-----	-----

OR Odds ratio, CI Confidence interval, HS-CRP High sensitivity C-reactive protein,
LDH Lactate dehydrogenase, WBC White blood cells, NLR Neutrophil to lymphocyte ratio

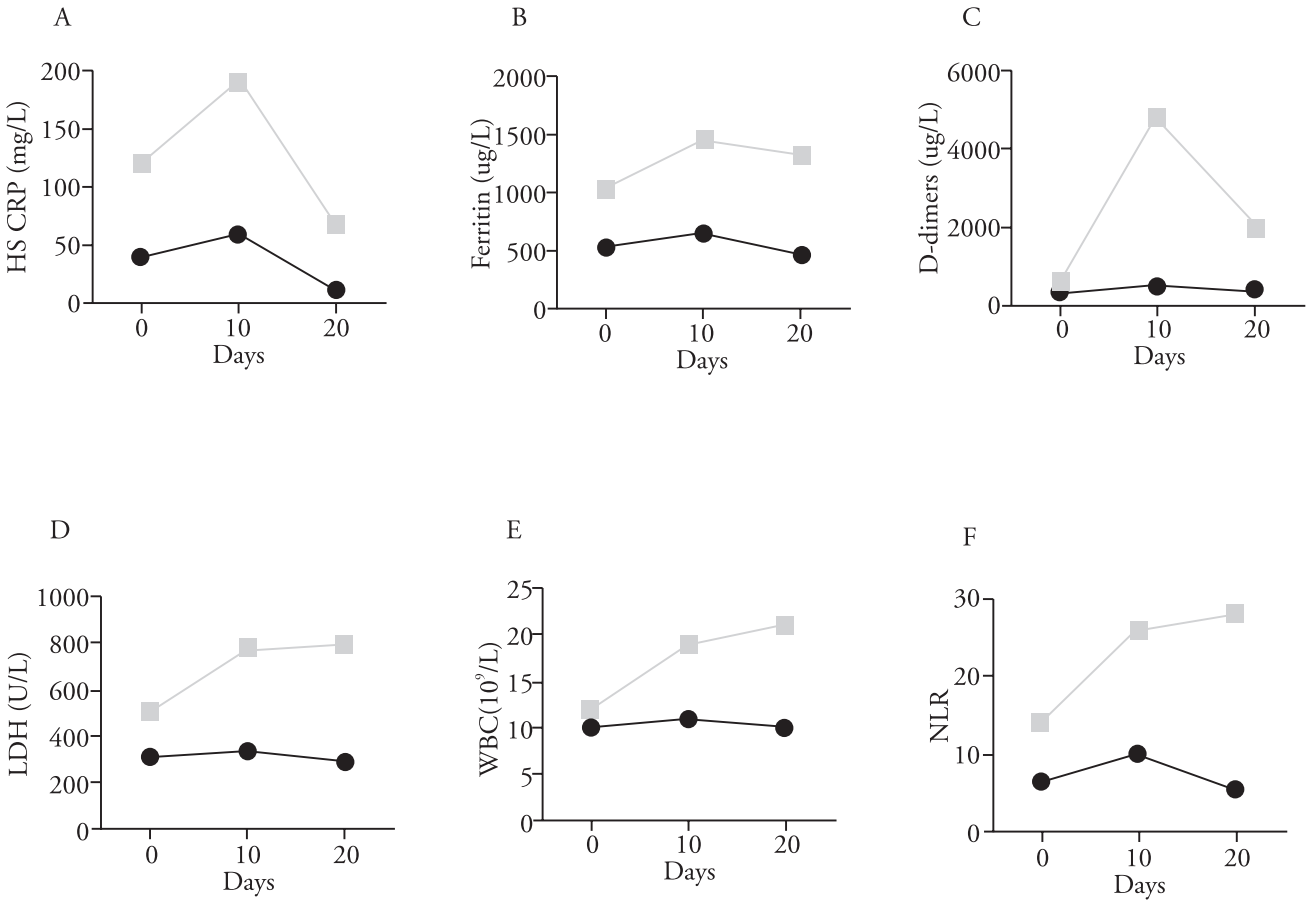

Figure 1: Three-time point estimation of inflammatory markers in deceased and recovered patients
Three-time point estimation (median) of inflammatory parameters in deceased and recovered patients. The levels of HS-CRP (A), Ferritin (B), D-Dimers (C), LDH (D), WBC (E), and NLR (F) in deceased (Red Square, N = 51) and recovered patients (Blue Circle, N = 65) were determined at three-time points i.e. on day 0, on day 10, on day 20. HS-CRP: High sensitivity C-reactive protein, LDH: Lactate dehydrogenase, WBC: White blood cells, NLR: Neutrophil-lymphocyte rat

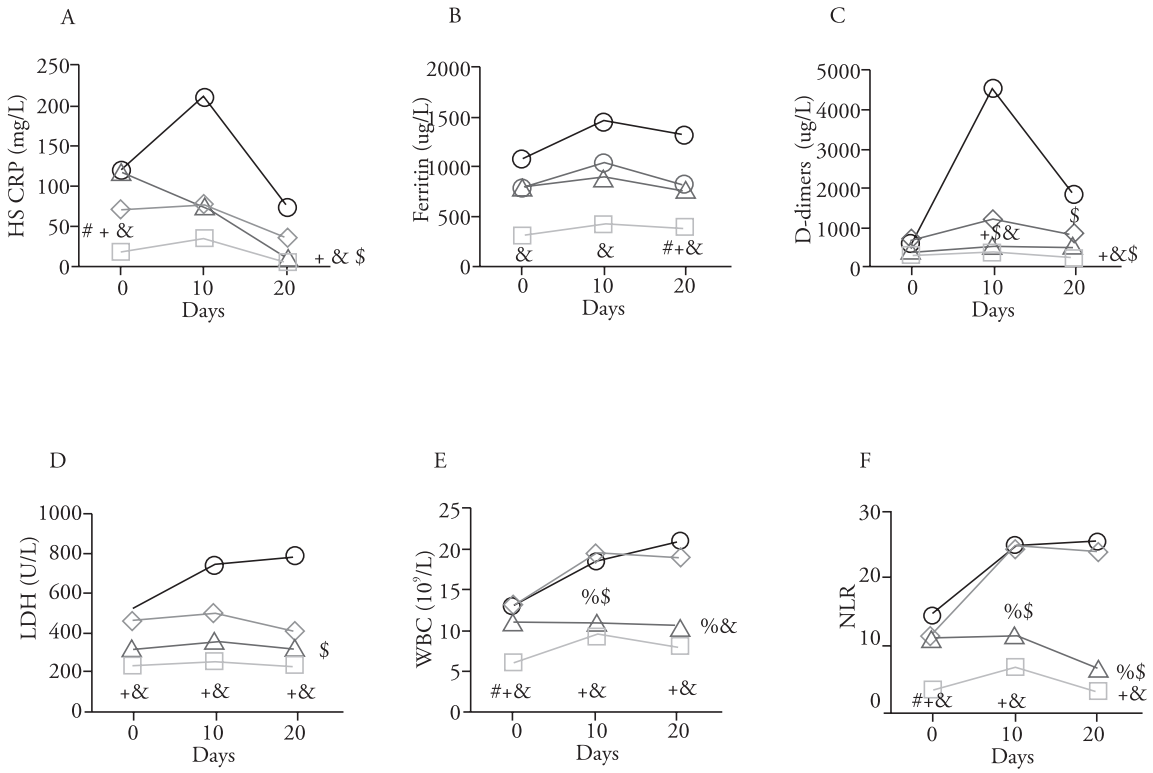

Figure 2. Three-time point estimations of inflammatory markers on the basis of disease severity.
The levels of HS-CRP (A), Ferritin (B), D-Dimers (C), LDH (D), WBC (E)), NLR (F) in Critical (Red circle, N = 46), Severe (Blue crystal, N = 14), Moderate (Black Triangle, N = 28), Mild (Purple Square, N = 28) at three-time points i.e. on day 0, on day 10 and on day 20 on Kruskal Wallis test. # = Significant difference between mild and moderate, + = Difference between mild and severe, & = Difference between mild and critical, % = Difference between moderate and critical while $= Difference between moderate and critical categories. HS-CRP: High sensitivity C-reactive protein, LDH: Lactate dehydrogenase, WBC: White blood cells, NLR: Neutrophil- lymphocyte ratio.

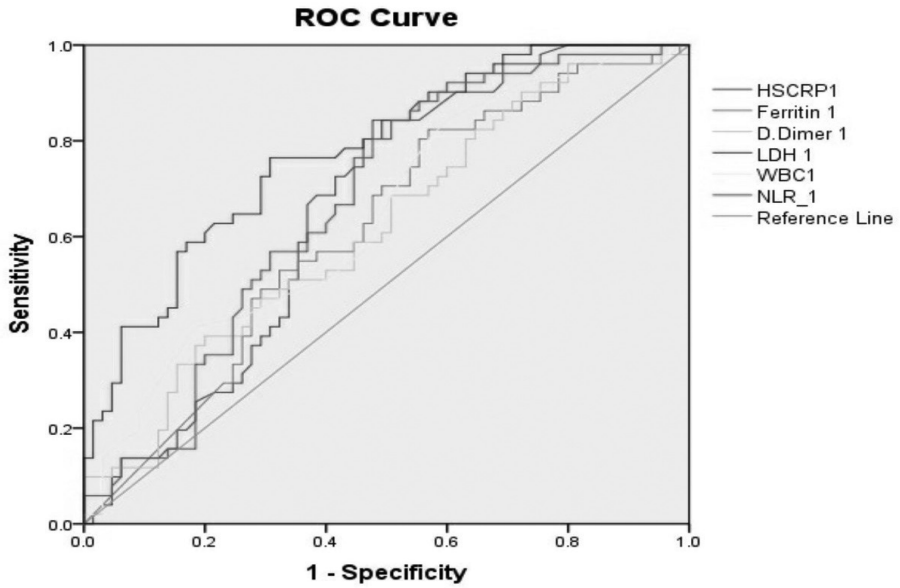

Figure 3. ROC curve of inflammatory parameters on admission (day 0) HS-CRP: High sensitivity C-reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil-lymphocyte ratio, Suffix1: On admission day or day 0

Our study showed that diabetes mellitus and hypertension were among the most common comorbidities with 76.5% and 74.5% incidence in deceased subjects respectively. The incidence of diabetes in our subjects was more than twofold than that of Sharifpour (31.3%) and Zhou (31%) et al. The incidence of hypertension was comparable to that of Sharifpour et al (82.1%). The incidence of ischemic heart disease (39.2%) in deceased subjects was almost twice the results shown by Sharifpour et al (20.9%). On the other hand incidence of CKD (5.9%) was much lower than that of Sharifpour et al (17.9%).

In deceased individuals, the median values of HS-CRP, Ferritin and D-dimer were highest on day 10 and declined on day 20 while levels of LDH, WBC and NLR were constantly rising from day 0 till day 20 depicting the predictive ability of LDH, WBC and NLR as compared to HS-CRP, Ferritin and D-dimer. This fact is evident in Table 2 and Figure 1. WBC and NLR along with LDH showed a constant and gradual rising trend at all three-time points in the critical category. This points towards the fact that a constant rising pattern of these markers should be taken into consideration while treating severe and critical patients. The constant rise of LDH in the critical category was also reported by Zeng et al.[14]

The univariate, multivariable logistic regression analysis revealed that old age, NLR and LDH on admission and comorbidities like diabetes mellitus and ischemic heart disease were predictors of mortality. The risk predictive ability of NLR was also established by Maddani and co-workers.[18] Our findings regarding LDH were consistent with the conclusion drawn by Zeng et al.[14] Asghar et al[19] in their study also concluded the risk predictive ability of LDH. Similarly Jusufovic[20] and colleagues inferred the same results regarding LDH. According to the present study, LDH level of 312U/L on admission or more can be predictive of adverse or poor outcomes. Zeng et al[14] concluded that LDH levels of >400 U/L on admission were associated with disease severity.

Like our study, the risk prediction ability of diabetes mellitus was also concluded by Hadith Rastad et al[21] and Kyounget and colleagues.[22] The ability of ischemic heart disease to predict the mortality was consistent with the finding of Tian Gu, et al.[23]

CONCLUSIONS

The study concluded that serial estimations or three-time point estimations of inflammatory markers and especially serial estimations of LDH, WBC count and NLR correlated well with disease severity and poor outcomes in patients having covid-19 infection. The old age, NLR and LDH on admission, and comorbidities like diabetes mellitus and ischemic heart disease correlated significantly with mortality. The LDH more significantly correlated with poor outcomes among other markers. At the time of admission, a value of 312 U/L or higher of the marker can be important in the assessment of risk prediction.

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Author's Contribution

MH conceived the idea, designed the study, performed data analysis and helped in the write up of the manuscript. SO helped in designing the study and helped in the write up of the manuscript. SZ and NS performed data analysis. MMD and AI helped in the write up of the manuscript. All authors made substantial intellectual contributions to the study.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.