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A RETROSPECTIVE STUDY TO EVALUATE THE ROLE OF LABORATORY BIOMARKERS IN DETERMINING THE DISEASE SEVERITY AND EARLY DETECTION OF PROGRESSION TO ADVANCED STAGE IN COVID 19 PATIENTS

KEY WORDS: COVID-19, D.dimer, S.Ferritin, Lymphopenia

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ABSTRACT

Novel corona virus epidemic started in Dec 19 in Wuhan, China and soon it spread globally and became an international emergency Our objective was to study the role of hematological and biochemistry markers in assessing the disease severity and prognosis of laboratory confirmed, hospitalized Covid 19 patients. 130 patients were included in this cross-sectional retrospective study and divided into mild/moderate and severe/critical group. Correlation analysis was done for laboratory biomarkers. We found that mean age, lactate dehydrogenase (LDH), S. ferritin, urea, uric acid, D-dimer and S.creatinine of severely ill patients were significantly higher than those of patients with non-severe illness. Leucopenia and neutropenia were also associated with disease severity. Males were affected more than females with both mild and severe illness. Following parameters like S. Ferritin, LDH, TLC, neutrophil % can help in identifying the progression of disease from mild to severe and help in adopting appropriate measures in the management so that progression can possibly be prevented. Rising levels of some parameters like D.dimer, urea, uric acid and creatinine also help in explaining the prognosis of patient.

INTRODUCTION

The first case of SARS-Corona virus -2 in India was reported in Kerela on Jan 27, 2020. By Sep, 20 USA and India were leading in the number of positive cases, USA having a death toll of 199746 and 83198 in India. [1] The disease spread like fire and strict lockdowns were imposed all over the world. Need arose of identifying predictors which could predict the course and slippage into advanced stage of disease. This disease involved not only lungs but also multiple organs like cardiovascular system, kidneys, liver, central nervous system and blood coagulation profile. We conducted this study from September 20 to January 21 and selected 130 cases for this study. Through this study we have tried to identify those parameters which can help in distinguishing those patients likely to develop severe form of Covid 19. This not only helps in stratifying patients into different risk groups for management but also puts less burden on resources by proper allocation of human and financial resources in a time when all of them were adversely impacted in majority of nations of the world.

METHODS

We conducted a cross-sectional observational study on patients admitted in various disciplines of our institution. Only 130 patients hospitalized during the period September 20 to January 21 were selected for this study. Nasopharyngeal/oropharyngeal swabs were collected and only those confirmed positive for SARS-CoV-2 by RT-PCR were enrolled. Blood samples were collected and hematological and biochemical analysis done. All the laboratory data was collected at the time of admission of patients. Covid 19 RT-PCR was performed on Biorad CFX 96 analyser

Hematological parameters like complete blood count were done on EDTA samples on Sysmex Xs-800i. Biochemical parameters like creatinine (Cr), alanine aminotransferase (ALAT), aspartate aminotransferase(ASAT), total bilirubin (TB)were done on Turbochem 100 automated biochemistry analyzer. Lactate Dehydrogenase (LDH), ferritin were obtained through Cobas 6000 (Roche)/Elecsys 2010. D-Dimer(DDIM)) was evaluated on STA-R Evolution® analyzer (Stago, France) on citrated plasma Patients were divided into two groups based on clinical presentation and according to a management needed in accordance with WHO guidelines and Indian Covid treatment guidelines, so that different hematological and biochemical parameters can be compared. Group A comprised of non-severe patients with mild to moderate symptoms who were admitted in isolation wards and Group B comprised of severe to critical patients who were admitted in intensive care unit. Verbal consent was taken. This study was reviewed and approved by ethical committee of our institution.

RESULTS

A total of 130 patients with confirmed SARS-CoV-2 infection were enrolled in this study and classified into two groups A and B based on clinical presentation. Group A comprised of 75 patients with mild/moderate symptoms and group B comprised of 55 patients with severe/critical symptoms. The p value of <0.05 was considered significant, <0.001 as highly significant and >0.05 as non-significant.

Table 1. Demographic and clinical characteristics of patients.

Characteristics	Total (n = 130)	Severe (n = 55)	Non-severe (n = 75)	P-value
Age (years)	57 [22–88]	56 [26–85]	58 [22–88]	
Sex				
Male	89 (68.5%)	34 (62%)	55 (72%)	0.026
Female	41 (31.5%)	21 (38%)	20(28%)	0.875

Leucopenia and neutropenia was noted as the disease progressed. Lymphocyte count was higher in group B when compared to group A. Hematological profile revealed lower mean neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in group B than group A.

Table 2

	Mild	Severe	Overall
NLR	3.08	2.47	2.80
PLR	0.09	0.08	0.09

Correlations were noted for S. ferritin, Urea, LDH, MCHC, calcium, globulin, Direct and total bilirubin. As the disease progressed, a reverse correlation was seen with LDH, Creatinine, sodium, potassium, chloride, Albumin, total bilirubin, Hemoglobin, Neutrophil count, TLC, Platelet, PCV, MCV, MCH, RDW-CV

Table 3. Correlation and p- value

VALUE	Overall		Mild		Severe	
	R	p-value	R	p-value	R	p-value
S. Ferritin	0.34	0.03	0.28	0.024	0.033	0.82
LDH	-0.13	0.044	-0.05	0.86	-0.15	<0.05
Urea	0.23	0.026	0.003	0.984	0.313	0.02
Creatinine	-0.009	0.932	-0.023	0.887	-0.024	0.865
Uric Acid	0.037	0.721	0.153	0.333	0.021	0.878
Na	-0.004	0.973	0.191	0.226	-0.005	0.974
K	-0.013	0.903	0.22	0.161	-0.01	0.94
Cl	-0.073	0.483	0.13	0.412	-0.104	0.451
Ca	0.12	0.249	-0.052	0.745	0.188	0.169
Total	-0.015	0.89	-0.354	0.022	-0.006	0.966
Direct	0.002	0.982	-0.394	0.01	0.031	0.821
Indirect	-0.034	0.744	-0.262	0.094	-0.053	0.7
SGOT	0.088	0.4	-0.079	0.617	0.138	0.316
SGPT	0.006	0.954	0.043	0.787	0.046	0.738
ALP	-0.008	0.938	-0.1	0.529	-0.005	0.97
total protein	0.059	0.574	-0.119	0.453	0.096	0.486
Albumin	-0.003	0.979	-0.078	0.623	0.015	0.916
Globulin	0.104	0.317	-0.139	0.38	0.132	0.336
A/G ratio	-0.069	0.509	0	0.999	-0.074	0.591
Hb	-0.101	0.331	-0.014	0.93	0.143	0.299
Neutrophils	-0.096	0.358	-0.287	0.065	-0.114	0.409
Lymphocytes	0.021	0.844	0.281	0.071	0.013	0.927
TLC	-0.054	0.608	-0.163	0.303	-0.06	0.664
PLT	-0.097	0.354	-0.056	0.722	0.115	0.403
ESR	-0.342	0.095	-0.527	0.079	0.347	0.245
RBC	0.005	0.963	0.019	0.905	-0.007	0.962
PCV	-0.019	0.857	0.005	0.976	0.004	0.978
MCV	-0.026	0.8	-0.101	0.527	-0.031	0.821
MCH	-0.02	0.852	-0.036	0.819	-0.039	0.776
MCHC	0.005	0.964	-0.331	0.032	0.005	0.973
RDW-CV	-0.033	0.752	-0.166	0.293	-0.022	0.876

DISCUSSION

In our study, disease severity was correlated with hematological and biochemical parameters and their significance was noted. Patients demographic characterstics in our study have shown that increasing age is associated with severity of disease, this has been corroborated by other studies as well [2,3]. Advanced age was also reported as an important independent predictor of mortality in SARS and MERS [4,5,6]. Males have been associated more with severe spectrum of disease in our study, this is also supported by other authors [7] however a study from Iran says that sex is not related to disease severity [6]. The median age of patients enrolled in our study was 57years (range 22-88 years). A much lower median age has been reported by Huang et al [8]

Increase in LDH levels seen in our study has been supported by Liu who correlated LDH, lymphocyte, neutrophil levels with severe COVID pneumonia [9]. Terpos et al also reported higher LDH in 41% of his patients. He also pointed out that increased mortality, higher chances of ICU support and increased risk of acute respiratory distress is associated with higher LDH levels.[10] Higher S. Ferritin levels seen with aggravation of disease is related with cytokine release associated with multiple organ failure as reported by Liu Y and Lu J. [9, 11].

Rise in D-Dimer value noted is also associated with progressive disease and resulted in thromboembolic phenomena. This is consistent with Lu J's study,[11] similar results were also obtained by Razanamahery J and Sun S et al. [12,13] Significant anemia and thrombocytopenia were not observed in our enrolled patients like other studies.[14, 15] Leucopenia and neutropenia observed in our study was also reported by other authors.[16] In our study, lymphopenia was seen in 41% (31/75) of mild cases and 18% (10/55) of critical patients. A higher incidence of lymphopenia was reported among critical cases in a study done in Singapore.[17] In our study, lower NLR and PLR was seen in group B patients especially those manifesting severe disease which is in contrast with other studies [18,19] S.Urea showed significant association with Covid 19 severity like study done by Agarwal et al.[19] In addition , ESR, Calcium, Hemoglobin, Globulin were also related to disease severity which collaborates with other research studies.[20,21,22]

Several factors posed as limitations in our study. First is the relatively small cohort of patients included in the study. Ours was a retrospective design of study conducted in a single centre. This increases the selection bias and adversely affects the generalizability of results. Second some patients were in isolation/general wards but were advised critical care according to WHO criteria. [23] They failed to shift either due to paucity of beds or financial difficulties. Third limitation in lack of conduction of some laboratory tests in some patients especially those with higher costs like ferritin, procalcitonin, IL-6, D-Dimers etc and body mass index evaluation. These factors have affected statistical analysis. A prospective study with larger sample and exclusion of patients who were not in ICU though advised according to admission guidelines is needed.

CONCLUSION

On analyzing different biochemical and hematological parameters in both mild and critical group it was observed that these parameters showed little deviation in the mild group and hence considerable changes in their values can point towards disease progression. Periodic assessment of D-dimer, S. ferritin, LDH, S. urea values are important for follow up of these patients and thus can guide towards early intervention and altering the disease outcome.

Conflict of interest

The authors have no conflicts of interest

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