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Pathology

Utility of Routine Clinical Laboratory Tests in COVID 19

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Abstract **Original Research Article**

The novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection leading to COVID-19 pandemic has affected many countries all over the world including India. Diagnostic laboratories play crucial role in containment of pandemic as they enable the rapid identification for isolation and treatment of COVID-19 positive cases. Gold standard test for COVID 19 detection is the reverse transcriptase Polymerase Chain Reaction (RT-PCR)-based assays performed on respiratory specimen. The role of other laboratory parameters in COVID-19 cases has not been definitely established. Clinical laboratory investigations need to be studied in larger populations to understand the pathogenesis and to understand whether these parameters are useful to triage COVID-19 suspect patients before the results of RT PCR are available. This study was aimed to analyze and compare routine clinical laboratory parameters in COVID-19 positive and negative patients at the time of presentation to our tertiary care referral center situated in western region of India from April, 2020 till November, 2020. Patients were divided into two groups based on the results of RT-PCR for COVID-19. The outcome of different laboratory parameters like CBC, CRP, AST, ALT, LDH, ferritin were evaluated in cases with positive RT-PCR and compared with negative RT-PCR group. We found no statistically significant differences between COVID-19 positive and negative group on routine clinical laboratory parameters of 4602 patients.

Keywords: COVID-19, Investigations, Laboratory, Pandemic, RT-PCR.

INTRODUCTION

In year 2020 almost all countries were affected by a pandemic disease COVID19 caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged in Wuhan, Hubei, China at the end of December 2019 [1]. The primary goal adopted by governments all over the world for containment of the epidemic of COVID-19 is to reduce the infection transmission in the population by reducing the number of susceptible persons by quarantine or by reducing the basic reproductive number (R0) [2, 3]. The occurrence, development, pathogenesis and immune status of patients with COVID-19 are still under research [4]. Most effective method to reduce SARS-CoV-2 transmission is to identify and isolate infected patients who are contagious and can transmit the disease [3]. Diagnostic laboratories play crucial role in containment of pandemic as they enable the rapid identification for isolation and treatment of COVID-19 positive cases. Gold standard test available currently are the reverse transcriptase Polymerase Chain Reaction (RT-PCR)-based assays performed on respiratory specimens [2]. For rapid diagnosis of SARS-CoV-2 infection, qualitative rapid antigen detection tests (RAT) which detect viral antigen by the immobilized coated SARS-CoV-2 antibody on the device are available [5]. Many researchers have studied the clinical features and imaging findings of COVID-19 along with the diagnostic and prognostic value of abnormal laboratory findings [6]. Most

frequent abnormalities noted in laboratory parameters in COVID-19 patients are increased aspartate aminotransferase (AST), leukopenia, decreased lymphocyte count, increased lactate dehydrogenase (LDH), increased C-reactive protein (CRP), and increased alanine aminotransferase (ALT) [2]. Various immune parameters are found helpful to identify risk of unfavorable course of the disease, predict the prognosis and recognize improvement in the clinical status and to find novel prospective therapeutic strategies [7]. However majority of these studies have limitations such as low sample size, different applied methods, dissimilar reference ranges, non-synchronized methods of representing the results, and variety in the panels conducted [6]. Clinical laboratory investigations need to be studied in larger populations to understand the pathogenesis and to understand whether these parameters are useful to triage COVID-19 suspect patients before the results of RT PCR are available.

This study was aimed to:

a. Analyze the trend of routine clinical laboratory parameters in COVID-19 positive patients at the time of presentation to hospital
b. Compare the clinical laboratory data between COVID positive and COVID-19 negative group.
c. To determine the correlation between various parameters in clinical laboratory data.

MATERIALS AND METHODS

In this retrospective observational study, we analyzed the blood test results of 4602 COVID-19 suspect patients who presented to fever clinic and were tested for RT-PCR and other blood investigations in our tertiary care center located in Mumbai, Western India from April, 2020 till November, 2020. The values of complete blood count (CBC) and Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin, qualitative C-reactive protein (CRP) on samples drawn at the time of presentation to the hospital were analyzed. The patients were divided in two groups based on RT-PCR result as Covid-19 positive (RT-PCR positive) and COVID-19 negative (RT-PCR negative).

RESULTS

RT PCR testing was advised to all 4602 patients after evaluation as per the guidelines regularly being issued by ICMR COVID 19 testing strategy [8]. Mean age of all the patients presenting to fever clinic was 50.6 years (range 1 year to 94 years). 2592 were male and 2010 were female patients. 30% (1360) patients tested positive for COVID-19 by RT-PCR results (positive group) and 70% (3262) patients had negative RT-PCR result (negative group). The positive group was composed of 848 males and 512 females (average age 53and 52 years for the male and female respectively), whereas the negative group was composed of 1744 males and 1498 females (average age 52 and 48 years for the male and female respectively).

Table I: Male and female distribution and mean age in Positive and Negative group

	COVID 19 POSITIVE		COVID 19 NEGATIVE	
	n	**Average Age**	**n**	**Average Age**
Male	848	53	1744	52
Female	512	52	1498	48
M:F ratio	1.6		1.16	
Total	1360	52	3242	50

(n= number of patients)

Routine blood investigations were ordered simultaneously at the time of presentation to fever clinic for these patients. The mean with standard deviation of the results obtained were calculated using Excel software. Comparisons of the analyte levels between the positive and negative groups were performed using a two-tailed, unequal variances t-test (Welch test). Differences between the COVID-19-positive and -negative groups were considered statistically significant if the p-value was lower than 0.05.

Table II: Averaged CBC and other biomarkers and corresponding standard deviation in Positive and Negative group

Parameter	Unit	POSITIVE GROUP		NEGATIVE GROUP		p- value
		Mean (n)	SD	Mean (n)	SD	
TLC	X 10^9 cells/L	6.88 (1347)	3.14	8.16 (3213)	3.66	-12.01
Lymphocyte	X 10^9 cells/L	1.73 (1287)	1.10	1.96 (3149)	0.95	-6.71
Neutrophils	X 10^9 cells/L	4.45 (1230)	2.77	5.34 (2906)	3.40	-8.78
Eosinophils	X 10^9 cells/L	0.15 (884)	0.24	0.22 (2568)	0.28	-6.46
Lymphocyte percentage	%	27.07 (1323)	11.47	26.38 (3194)	11.46	1.86

Neutrophil percentage	%	63.85 (1323)	12.85	64.64 (3192)	13.00	-1.87
NLR	%	3.77 (1230)	0.11	4.18 (2906)	0.08	-121.95
Platelets	X 10^9 cells/L	239.81 (1347)	91.72	258.61 (3213)	98.31	-6.18
PLR	%	239.81 (1347)	91.72	258.61 (3213)	98.31	-6.18
PDW		12.84 (1248)	2.78	12.82 (2998)	3.00	0.23
Hb	Gm%	13.04 (1348)	2.06	12.67 (3214)	2.21	5.44
RDW		13.99 (1330)	1.95	14.17 (3192)	1.98	-2.82
AST	U/L	38.74 (1113)	34.93	40.33 (2575)	68.04	-0.93
ALT	U/L	38.30 (1126)	39.22	40.10 (2621)	75.16	-0.96
LDH	U/L	422.37 (140)	177.27	458.33 (288)	343.65	-1.43
Ferritin	Ng/ml	174.97 (273)	271.24	221.85 (572)	468.01	-1.84

(**Abbrevations:** n= number of patients, TLC- Total leukocyte count, NLR- Neutrophil to lymphocyte ratio, PLR- Platelet to lymphocyte ratio, PDW- Platelet distribution width, Hb- Hemoglobin, RDW- Red cell distribution width, AST- aspartate aminotransferase, ALT- alanine aminotransferase, LDH- Lactate dehydrogenase)

When compared with negative group mean values, positive group apparently showed higher mean values of hemoglobin, platelet distribution width, lymphocytosis and lower values of leukocyte count, neutrophil, eosinophil count, platelet count, RDW, AST, ALT, LDH and ferritin. However, the difference between the mean values in positive and negative group was not statistically significant (p value > 0.05).

Qualitative C reactive protein was found to be positive in 35% (143) patients in positive group (n=405) and in 34.7% (267) patients in negative group (n=768).

Correlation analysis was performed using 'Statistical Methods' by Snedecor and Cochran [9] to assess interdependence/ association between laboratory parameters in positive group. Clinically significant observations with significant T value corresponding to P value of <0.01 and <0.05 were analyzed.

Table III: Correlation coefficients of clinical laboratory parameters in COVID-19 positive patients.

Associated of parameters		Correlation Coefficient	% relation between the parameters
Leukocytosis	Lymphocytosis	0.48**	22.6
Leukocytosis	Neutrophilia	0.91**	83.4
Leukocytosis	Raised Ferritin	0.51**	26.1
Lymphocytosis	Raised AST	0.83**	68.6
Lymphocytosis	Raised ALT	0.68**	46.8
Lymphocytosis	Raised LDH	0.50**	25.4
Neutrophilia	Raised Ferritin	0.59**	35.2
NLR	Raised Ferritin	0.41*	16.9

** Significant at 1% level of significance
* Significant at 5% level of significance

The results indicated that rise in total leukocyte count was associated with rise in peripheral blood neutrophils in 83% COVID-19 positive patients. Rise in neutrophil counts and NLR was accompanied by rise in serum ferritin levels and lymphocytosis was associated with raised AST, ALT, LDH in COVID-19 positive patients.

DISCUSSION

We observed slight male predominance (1.60) in COVID-19 positive patients and mean age of females was lesser than that of males. Studies by Gao *et al*., (n=43) [4], Mohan A *et al*., (n=144) [10] from China and India respectively have also reported male predominance.

Studies support that SARS-CoV-2 virus particles spread through the respiratory mucosa and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral WBCs and immune cells such as lymphocytes. Consumption of immune cells leads to inhibition of body's immune function [4]. Substantial numbers of clinical studies have reported lymphopenia in patients with confirmed COVID-19 infection and also shown to be associated with pneumonia especially in elderly patients [7]. Lu *et al*., (China) found that dynamic changes in hematological parameters like leukocyte count, neutrophils, eosinophils, RDW, NLR and platelet lymphocyte ratio could be helpful for the prognosis of COVID-19 patients [11]. We observed a lower total leukocyte count and lymphocytosis in positive group when compared to negative groups. None of the hematological parameters were statistically significant for prediction of COVID-19 positive status. Wang *et al*., (China) found that the combined NLR and RDW-SD parameter as the best hematology index to predict the severity of COVID-19 patients [12]. We could not establish relationship between NLR and other hematological parameters in COVID-19 positive patients.

Studies by Ferrari *et al*., (Italy) [1], Gao *et al*., (China) [4] and few others have reported that decreased albumin, increased lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, cardiac troponin, D-dimer, procalcitonin, and CRP are associated with the unfavorable progression of COVID-19 [7]. C-reactive protein (CRP) produced by the liver, is an acute phase reactant that is increased in a wide range of inflammatory conditions. Frater *et al*., (USA) reported increased CRP in 75-93% of patients with COVID-19 infection [13]. We observed positive CRP in 35% patients with COVID-19 infection and almost an equal number (34.7%) in patients who were COVID-19 negative. This implies the inflammatory response is non-specific as to etiology of the disease. Considering that lower number of the COVID-19 positive had positive CRP, the severity of the disease was mild in majority of patients at the time of presentation to the hospital.

Observations of this study did not show any statistically significant difference between COVID-19 positive and negative groups for various laboratory parameters. However, COVID-19 positive patients showed positive association between hematological parameters and biomarkers. In the positive group lymphocytosis was associated with raised AST, ALT and LDH. Neutrophilia and raised NLR were associated with raised serum ferritin levels. The study of 144 Indian patients by Mohan *et al*., also did not report any significant difference in baseline laboratory parameters such as haemoglobin, TLC, lymphopenia, NLR, platelet counts, urea, creatinine, total protein, albumin, bilirubin, ALT, AST or alkaline phosphatase between symptomatic and asymptomatic patients [10]. We observe that findings amongst Indian population are discordant from those reported in literature from China, Europe and USA.

To the best of our knowledge, this is the first study analyzing clinical laboratory parameters in COVID-19 infected individuals in Indian population from Western region with larger sample size [14]. This study has a limitation that the clinical parameters and underlying comorbid conditions and serial measurement of parameters with clinical progression were not included in the analysis.

CONCLUSION

We found no statistically significant differences between COVID-19 positive and negative group on routine clinical laboratory parameters of 4602 patients at the time of presentation to the healthcare facility. However, COVID-19 positive patients showed positive association of lymphocytosis with raised AST, ALT, LDH levels and neutrophilia and raised NLR with raised serum ferritin levels.

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Conflicts of Interest of each author/ contributor: NIL

Registration number in case of Clinical Trials: CTRI/2020/12/030053

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