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Demographic and laboratory comparisons among patients admitted during the first, second and, third waves of COVID-19 at Shri Vinoba Bhave Institute of Medical Sciences, Silvassa, India

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ABSTRACT

Introduction

COVID-19 has affected millions of people worldwide. In India from first case in March 2020 to till date it has made 3 peaks (waves) in active case.This study was aimed to compare different laboratory parameters among patients of these waves.

Aim

To compare hematological and biochemical parameters among the patients admitted in different waves of Covid-19 in the study.

Material & Method

Patients of positive Covid-19 RTPCR admitted to SVBCH, Silvassa Dadra and Nagar Haveli were enrolled and data of the same were obtained from the hospital information system (HIS).

Results

Among all admitted covid 19 patients, we took 100 patients each in first and second wave and 99 patients from 3rd wave. In which total we took 164(55%) male and 135(45%) female. Mean age was 40years in second wave, which is higher in other two waves ($p<0.0001$). We found increased mean SGPT in first wave ($p<0.0001$), leukocytosis in third wave ($p<0.0001$) and other parameters like thrombocytopenia, increased polymorphs and increased D Dimer ($p<0.0001$) in second wave.

Conclusion

Most of the inflammatory markers were more severe during the early analysis of second wave. Severity of the disease was reduced during the third wave, due to virulence of the virus strain.

Keywords:

Keywords COVID-19, SAARS, RTPCR, SARS-CoV-2

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INTRODUCTION

Coronaviruses are enveloped, non-segmented, positive-sense RNA viruses belonging to the family Corona viridae and the order Nidovirales and broadly distributed in humans and other mammals. [1]COVID-19 has affected more than 236 million people worldwide, causing more than 4.8 million deaths as of October 6, 2021. [2] Total cases in India as on 19.12.2022 is 4,41,52,709 and deaths 5,30,745.[3] The first case of the disease was reported on 30 January 2020 in Kerala andsubsequently spread to other parts of the country.[4] In Rajkot, Gujarat, the first COVID-19 patient wasreported on 19 March 2020.[5]Initially, all the patients who tested positive for RTPCR testor were in contact with the COVID-19 positive patients with or without symptoms, were quarantined and treated. Later, the course of disease presentation varied during the first, second and third wave in terms of clinical pattern, severity and outcome ofthe disease. [6]Most studies of the clinical characteristics have primarily focused on patients from the first wave of COVID-19. Only a few studies have performed comprehensive investigations of the similarities and differences between hospitalized patients in different wave periods. [7, 8]The current study was planned to compare and identify differences in the demographic and laboratory characteristics of patients hospitalized in the three waves of COVID-19 outbreak. The comparison of different laboratory findings of these waves will be useful in early diagnosis and treatment, prevention and control of disease complications in India and beyond.

Aim

Comparison among 3 different waves of COVID-19

Objective

1.To compare demography and geography of the patients admitted in 3 different waves of Covid-19 in the study.

2.To compare hematological and biochemical parameters among the patients admitted in 3 different waves of Covid-19 in the study.

Material and methods

Study design and participants

This retrospective study was conducted at Shri Vinoba Bhavecivil hospital, Silvassa, DNH after obtaining institutional ethical committee approval.

1)To be included in the study, all patients admitted to the hospital at the time of respective wave, whose nasopharyngeal or oropharyngeal specimens were positive for severe acute respiratory syndrome ((SARS) CoV-2) RNA using real time polymerase chain reaction (RT-PCR) were considered as confirmed cases. Purposive sampling technique was used and 100 patients`data from each wave has been taken.None of the patient`s vaccination status for COVID-19 has been considered for this study.

Data sources

Data of age, gender, hematological parameters (complete blood count (CBC) and prothrombin time along with international normalized ratio (PT/INR)), biochemical parameters including Liver function test (total bilirubin TBIL, direct Bilirubin DBIL, indirect Bilirubin IDBIL, Serum glutamic pyruvic transaminase SGPT, Serum glutamic oxaloacetic transaminase SGOT, alkaline Phosphatase ALP, total protein TP, albumin ALB, globulin, A/G ratio), renal function test (serum urea level, Blood urea nitrogen, creatinine), serum electrolytes (Sodium, potassium, chloride), random blood sugar level (RBS) & inflammatory markers like interleukin, ferritin, CRP, were collected from hospital information system (HIS).

Measures

The biochemical parameters were estimated by using fully automated biochemistry analyzer Dimension EXL 200, Siemens and standard methods:

- Random Blood sugar (RBS) concentration was determined by hexokinase method.
- Serum blood urea nitrogen (BUN) was determined using urease and glutamate dehydrogenase.
- Serum creatinine (Cr) levels was determined with Jaffe's method
- The concentrations of total and direct bilirubin in the blood were determined by diazo method.

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- The activity of transaminases (SGPT & SGOT) was determined by a kinetic assay method
- Serum total protein (TP) was determined by Biuret and Albumin by BCG method.
- Serum Alkaline Phosphatase (ALP) activity in the blood was determined with p-nitrophenyl phosphate as a substrate.
- Serum electrolytes includes: Serum Sodium, potassium and chloride levels were determined by using ion selective electrode (ISE) methods.
- Hematological parameters including prothrombin time (PT/INR) by using Hemostar 4cA automated coagulation analyzer based on photo-electric principle and complete blood count (CBC) by using nihonkohden3 part analyzer based on electrical impedance principle. CBC includes erythrocytes (RBC, $x10^6/mm^3$) and leucocytes (WBC, $x10^4/mm^3$), hemoglobin (Hb, g/100mL; estimated by using cyanmethemoglobin method), hematocrit (packed cell volume, %), the mean corpuscular volume (MCV, μ^3), the mean corpuscular hemoglobin (MCH, pg) and the mean corpuscular hemoglobin concentration (MCHC, %). The last three parameters were calculated using the following formulas-

MCV= (packed cell volume as percentage/RBC in millions) x 10 μ^3

MCH = (Hb in g/RBC in millions) x 10 pg

MCHC = (Hb in g/packed cell volume) x 100 g per 100 mL

- CRP: particle enhanced turbidimetric immunoassay (PETIA) technique
- Ferritin: two-site sandwich immunoassay using direct chemiluminometric technology by Instrument: AdviaCentur CP.
- IL-6: one-step direct immunoassay using chemiluminescent technology by Instrument: AdviaCentur CP.
- D-Dimer: Turbidimetry by Instrument: Turbodyne SC.

A familiarization phase was completed prior to sample testing like calibrating all assays and then quality control (QC) samples were analyzed every time & only when they were within limits samples were analyzed.Study definitions.In India, the first wave began in March 2020 and lasted until nearly November 2020. The second wave started in March 2021 and continued until the end of May 2021,[9] although there is no direct evidence of a third wave, [10] many metro cities in India have reported a surge of new cases despite mass vaccination during January to March 2022.Initial laboratory data were defined asthe first available laboratory test result at hospital presentation.

Statistical analyses

Data were received and entered into Microsoft Excel 2019.

Data analyses were mainly descriptive. Continuous variables are presented as mean and standard deviation. Categorical variables are presented as counts (N) and percentages. The chi-squared test or Fisher´s exact test was used to compare differences in categorical variables. We tried to get missing data but if did not get then considered as nil report. A p-value belowo.05 was considered significant. All analyses were performed using Microsoft Excel 2019.

Results

Among all admitted covid 19 patients, we took 100 patients each in first and second wave and 99 patients from 3rd wave.

Table 1: Demographic characteristics of patients admitted with COVID-19 during the first, second and third outbreak

Characteristics	First Wave (n=100)		Second Wave (n=100)		Third Wave (n=99)		P-Value ANOVA
	Mean	SD	Mean	SD	Mean	SD	
Age in Years	32.24	15.37	40.16	15.51	30.03	15.45	0.000
Sex	No.	%	No.	%	No.	%	
Male	58	58.0 %	59	59.0%	47	47.5%	0.195
Female	42	42%	41	41%	52	52.5%	

As per the table 1, mean age in years in 3 waves of covid 19 were, 32.24±15.37, 40.16±15.51 and 30.03±15.45 respectively ($p<0.0001$). In the first and second waves, majority were males, 58% and 59% respectively, while in the third wave majority of patients 52.5% were female.

Table 2: Laboratory parameters of the COVID-19 cases in the first, second and third outbreak

Laboratory Findings	First Wave (n=100)		Second Wave (n=100)		Third Wave (n=99)		P Value (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	
Hematology Parameter							
ESR	20.63	11.81	34.28	18.61	16.21	6.89	0.000
HB (gms%)	12.50	2.31	12.26	2.12	11.60	2.73	0.025
TLC (1000/cumm)	7.66	3.41	8.74	5.02	7.25	3.21	0.025
RBC (mill/cumm)	4.47	0.77	4.56	0.78	4.24	0.69	0.009
Pcv (%)	38.22	9.10	36.32	5.67	39.88	7.42	0.004
MCV (fl)	84.46	12.51	80.80	10.78	82.35	10.56	0.073
MCH (pg/ml)	29.04	7.31	27.20	4.31	27.48	3.96	0.036
MCHC (gm/dl)	32.79	3.33	33.53	1.27	32.99	1.07	0.044
PLT (lac/cumm)	3.46	7.56	1.94	0.69	2.15	0.97	0.033
Polys (%)	63.36	15.97	74.20	11.32	62.41	19.21	0.000

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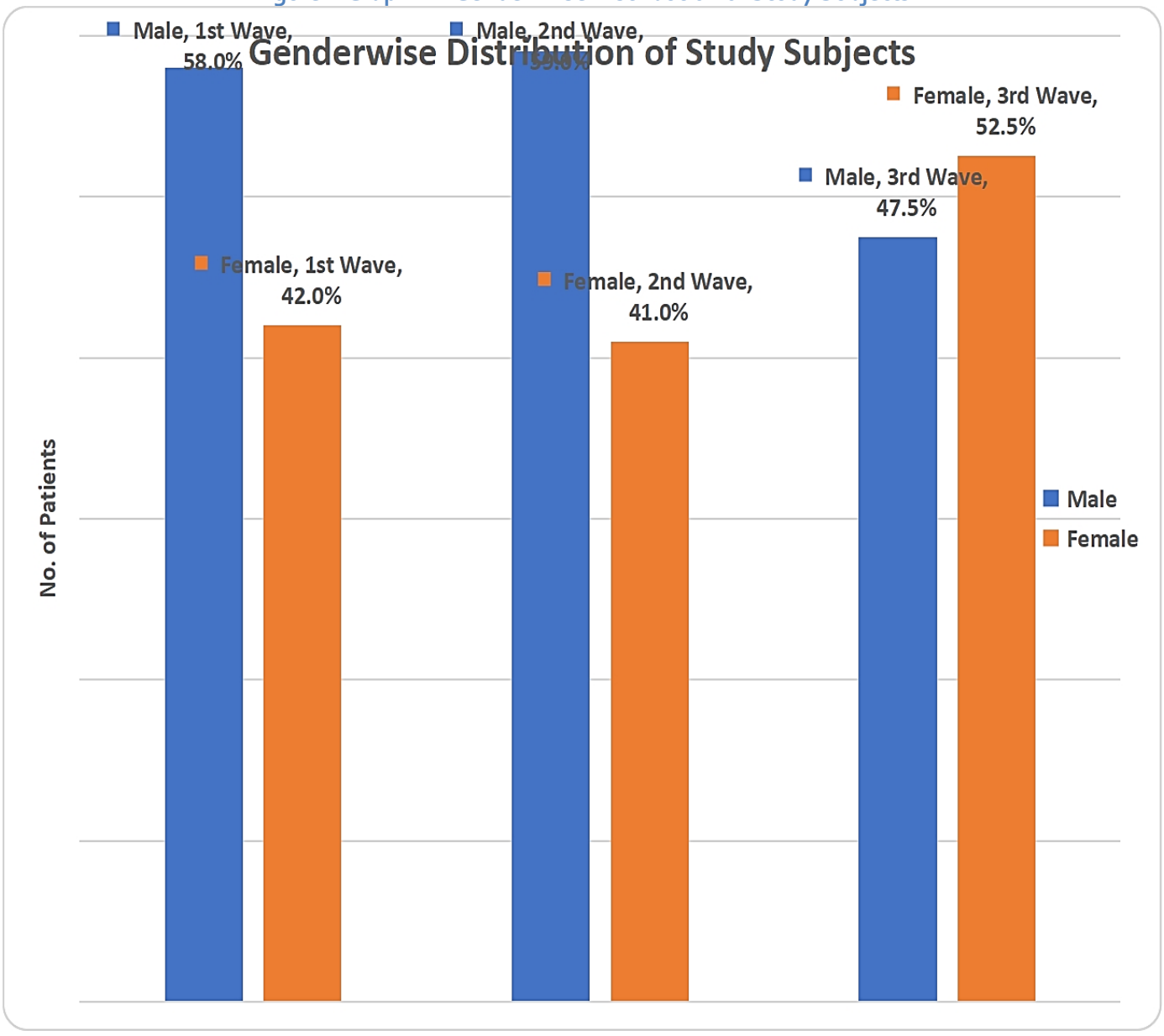
Lympho (%)	31.18	14.19	21.77	10.79	33.96	13.45	0.000
Eosin (%)	2.53	2.32	1.97	0.99	1.55	0.70	0.000
Mono (%)	2.10	1.24	1.66	0.77	1.42	1.09	0.000
Baso (%)	0.06	0.60	0.00	0.00	0.00	0.00	0.371
Biochemical parameters							
S. Bilirubin total (mg/dl)	0.77	1.58	0.57	0.45	0.56	0.20	0.218
S. Bilirubin direct (mg/dl)	0.15	0.19	0.22	0.17	0.21	0.15	0.008
S. Bilirubin indirect (mg/dl)	0.66	2.47	0.36	0.36	0.34	0.10	0.217
S.g.p.t (alt) (iu/l)	72.46	123.17	55.98	28.30	42.18	19.27	0.016
S. Alkaline phosphatase (iu/l)	113.21	69.92	107.92	104.87	71.17	5.80	0.000
S.g.o.t (ast) (iu/l)	43.99	38.67	54.18	31.59	38.33	17.92	0.001
ALBUMIN (gm/dl)	4.00	0.85	3.17	0.52	4.50	4.08	0.001
A/g ratio	1.26	0.50	0.89	0.23	1.32	0.22	0.000
SERIUM SODIUM (meq/L)	139.36	6.54	136.84	4.36	135.81	3.74	0.000
SERIUM POTASSIUM (meq/L)	4.44	0.85	4.51	1.35	4.30	0.52	0.300
SERIUM CHLORIDE (meq/L)	99.07	14.70	97.79	3.93	102.01	3.1	0.003
SERUM CREATININE (mg/dl)	1.09	1.18	0.92	0.42	0.89	0.5	0.15
BLOOD UREA NITROGEN (mg/dl)	13.29	11.57	16.44	9.81	15.98	8.76	0.061
BLOOD SUGAR (RANDOM) (mg%)	99.39	48.49	113.68	58.87	92.22	11.13	0.03
PT/INR (sec)	14.00	2.64	13.39	1.50	13.34	1.17	0.023

Inflammatory markers							
D-DIMER (ng/ml)	502.35	604.94	822.19	1999.72	109.58	64.61	0.000
INTERLEUKIN (ng/ml)	7.47	7.46	71.69	87.04	4.12	2.34	0.000
FERRITIN (ng/ml)	105.96	116.99	357.72	344.08	182.23	86.16	0.000
Crp– Quantitative (mg/dl)	19.90	26.92	61.41	64.91	5.53	2.92	0.000

Figure 1:Graph 01: Gender-wise Distribution of Study Subjects



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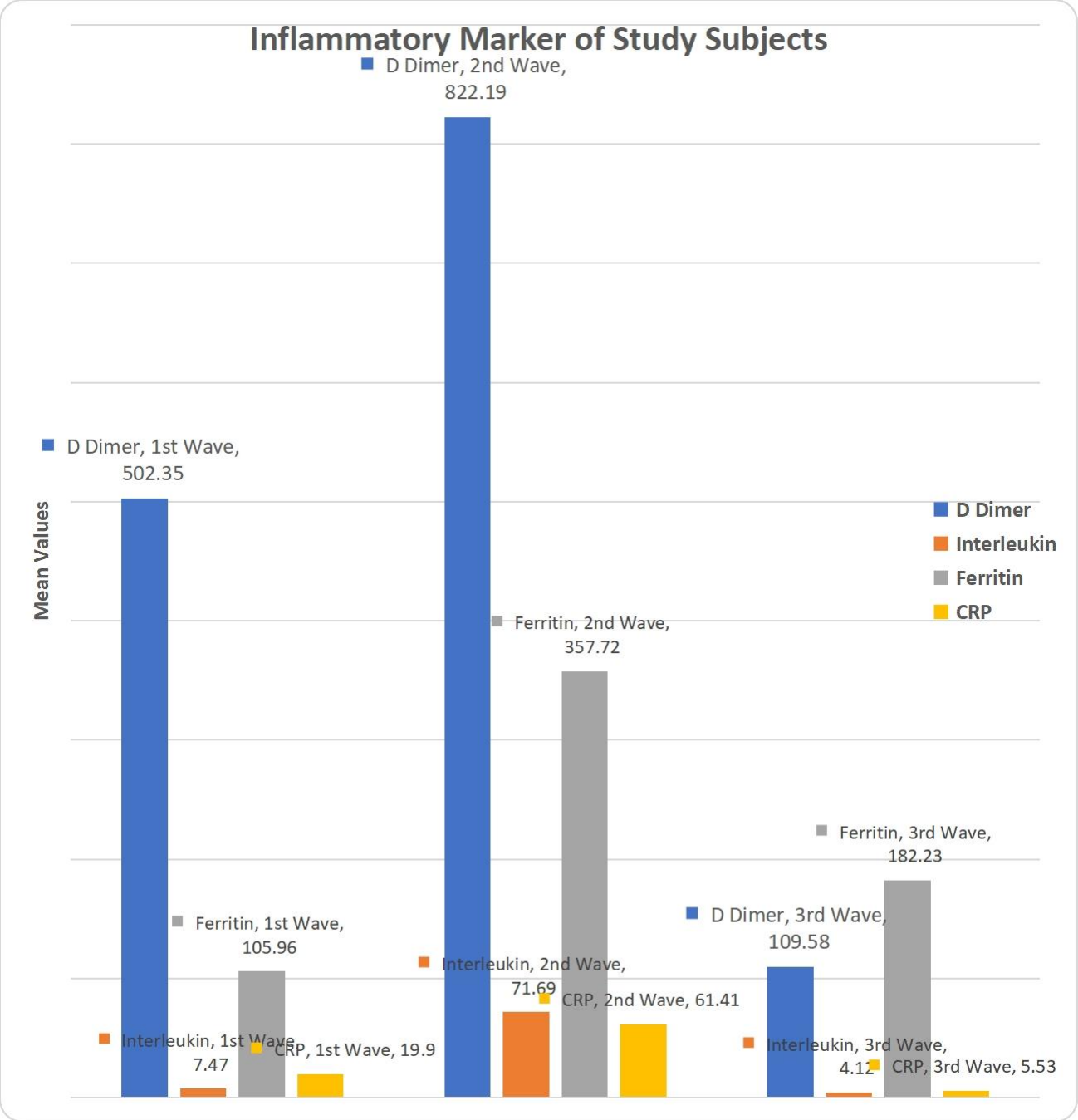
Graph 02: Inflammatory Markers of Study Subjects



We compared hematological, biochemical and inflammatory markers. In hematological parameters, we found a total leucocyte countof 8.74±5.02 (P = 0.025) in second wave, which was higher compared to the first and third waves. We found low lymphocyte count 21.77±10.79 (P = 0.000) in second wave as compared to first and third wave. During the second wave, polymorphs were higher, at 74.20±11.32 (P = 0.000) as compared to the first and third waves. We found low platelet count in second wave,1.94±0.69 (P = 0.033) as compared to first and third wave. All other parameters shown in table abovesignificantly differed between all three waves, except for the MCV. We observed a significantly raised ESR in the second wave, 34.28± 18.61 (P = 0.000), compared to the first and third waves.

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In biochemical parameter we found high SGPT 72.46±123.17 (P = 0.016) in first wave as compared to second and third wave. We found high SGOT 54.18±31.59 (P = 0.001) in second wave as compared to first and third wave. In our study S. Albumin was significantly reduced 3.17±0.52 (P= 0.001) in second wave as compared to first and third wave.In electrolyte, we found S. Sodium and Chloride significantly differ in all 3 waves but Potassium did not.We found high RBS (Random Blood Sugar) 113.68±58.87 (P = 0.03) in second wave as compared to first and third wave.The inflammatory markers were significantly higher, that was D-DIMER (P = 0.000), IL-6 (P = 0.000), serum ferritin (P = 0.000) and C-reactive protein (CRP; P = 0.000) in second wave as compared to first and third waves.

Discussion

The current study focuses on variations in laboratory findings upon admission among only hospitalized RTPCR confirmed COVID-19 patients. As compared to first and second waves, in the third wave more younger patients (<45 years) were admitted. More female patients were admitted in third wave as compared to first and second wave, otherwise male were predominating, may be due to lifestyle like smoking, health related self-care, active socialization or other factors. [8] Several studies reported that disease severity and mortality is worse in men. [11, 12].In our study, we found a higher leucocyte count in second wave with significant P value (0.025) in comparison to the first and third waves, with raised polymorphs (P = 0.000). Study done by Muhammad Sohaib et al [23] shows concerning the laboratory markers, total leucocyte count was equally affected during both waves but peak levels were attained early during second wave (P= 0.017). Study done by Muhammad Sohaib et al [23] also shows Neutrophil count was high on day 1 of the second wave (P = 0.001) and high peak levels were observed in the second wave (P < 0.001).In our study, we found lymphocytopenia during second wave as compared to first and third wave, with significant P value (P= 0.000). Study done by Muhammad Sohaib et al [23] shows lower lymphocyte on day 1 with persistently lower levels during second wave with significant P value (P < 0.001). In our study, we found low platelet count during second wave as compared to the first and third waves, with significant p value (P= 0.033). Study done by Muhammad Sohaib et al [23] shows platelet counts were similar during first and second wave except early attainment of lowest levels during the second wave with significant p value (P< 0.018).In our study S. Albumin was significantly reduced in second wave as compared to first and third wave, with significant p value (P= 0.001). Study done by Amira Mohammed Ali et al [24] also shows significant decrease in Protein was associated with severity of Covid 19.In our study high RBS (Random Blood Sugar) 113.68± 58.87 (P = 0.03) was associated in second wave as compared to first and third wave. According to the news published in TIMES "Coronavirus: COVID -19 Causes Blood Sugar Levels to Rise, Can Worsen Disease." [25]Inflammatory markers such as D-Dimer, CRP, Ferritin and IL-6 were the most important markers of the severity of COVID-19. They are independent predictors of severity and mortality. [13, 14] In our study, we found that levels of inflammatory markers such as CRP, IL-6 and ferritin were significantly higher in the second wave compared with the first and third wave. This demonstrates that patients with critical illness who were hospitalized in the second wave had more severe disease compared with the other two waves.According to the guideline published by the MoHFW on COVID 19, non- severe patients were hospitalized for at least 3–7 days to observe if the disease has worsened, and discharge criteria were stricter in the first wave than in the second wave. In the second wave, our national guidelines for the management of COVID pneumonia had changed, and Remdesivir was administered to hospitalized patients who worsened despite outpatient management.[15] In other words, during the second wave mild to moderate cases were managed in OPD. This could explain why inflammatory levels were higher in patients in the second wave than in the first wave.Rapid infection of young and naive populations in the second wave

could be due to viral mutation to the more devastating delta strain. The mutation in the virus had resulted in some of the most dangerous variants detected in India (UK strain:20I/501Y.V1 or B.1.1.7, South African 20I/501Y.V2 orB.1.351, Brazilian strain P. 1 and double mutant Indian variant B.1.617). [16,17]

Recent studies have suggested that, in addition to direct viral damage, uncontrolled inflammation contributes to disease severity in COVID-19.[18, 19] Consistent with this hypothesis, high levels of inflammatory markers, including CRP, ferritin, low neutrophils to lymphocyte ratio and increased levels of inflammatory cytokines and chemokines, have been observed in patients with severe diseases.[20, 21] Pathogenic inflammation, referred as cytokine storm, shares similarities with what was previously seen in patients infected with other severe corona viruses, including SARS-CoV and Middle East respiratory syndrome corona virus, and bears similarities to cytokine release syndrome observed in patients with cancer treated with chimeric antigen receptor modified cells.[22]The study has provided valuable insights into the viciousness of the second wave of the COVID-19 pandemic. The cases during the second wave of COVID-19 had higher inflammatory markers than the third wave. These results can be useful for further study like if use of antibiotics, immunomodulators and vaccination has any role for reduced inflammatory markers/cytokine storm or not. The implication of these findings is huge as the health policy makers need to be prepared to deal with these pandemics in terms of resources.

Limitation

One of the major limitations of this study is small sample size and single Centre hospital study. As the study is record based some of the missing data we couldn't retrieved. Also, we did not collect data on secondary infections and we took only at admission laboratory findings; follow up findings were not taken. We have not taken outcome parameters like whether patients were discharged or dead.Small sample size, single center hospital study, all kit reagents are not available at a time, data of secondary infection are also not collected are the major limitation of our study.

Conclusion

Most of the inflammatory markers were more severe during the early analysis of second wave, mean age was 40 years and majority were male. Only neutrophils were observed to reach higher peak levels during this time. Severity of the disease was more during the second wave, which might be due to the virulence of the strain "The Delta variant (or B.1.617.2 strain)" of the coronavirus in India.

By this study we can conclude that second wave of covid 19 was more serious in causing more changes in inflammatory marker like D-DIMER, Interleukin, ferritin, CRP etc. which are useful for prognosis purpose. During pandemic if unavailability of covid 19 RT PCR kit then this study is also helpful. These results can be useful for further study like if use of antibiotics, immunomodulators and vaccination has any role for reduction of inflammatory markers/cytokine storm or. This study is helpful for preparation of infection control manual, national policy for management of covid 19 pandemic etc.

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