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Original Research

C - Reactive Protein as A Predictive Biomarker in Assessing Severity and Progression of COVID-19

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Abstract:
Aim: The present study was done to find out the association of C-reactive protein (CRP) in prognosis and severity of SARS-CoV-2 infection in tertiary care teaching hospital.
Materials and methods: Present retrospective study was conducted for a period 3 years, 1000 patient samples were collected, including nasopharyngeal swab, oropharyngeal swab and serum samples. Swabs were subjected to real time RT-PCR (Reverse transcriptase polymerase chain reaction) for SARS-CoV-2; Serum samples were tested for C-Reactive Protein level estimation**.**
Statistical analysis: Data obtained in the study was analysed using SPSS statistics and Microsoft Excel 2019, in which CRP levels were studied in the COVID positive patients.
Results: From 1000 COVID-19 positive cases samples included in the study, 40.3% COVID-19 RT-PCR positive patients were with pneumonia, ARDS and co-morbidities such as obesity, hypertension, elderly age and chronic kidney diseases, from ICU, Triage and COVID positive wards. Amongst them, in 56.3% (n=227/403) patients, median CRP value observed was 185 mg/L with highest value of 318 mg/L, associated with severe complications leading to need of ventilation and even death of some.
Conclusion: C-Reactive Protein level could be helpful as predictive biomarker to assess severity in COVID-19, which is consistent with results of this study.
Key Word: COVID-19, C-Reactive Protein, SARS-CoV-2

Introduction:

Corona virus is known to cause mild to moderate respiratory tract infection with known outbreaks in 2003 as SARS-CoV and as MERS-CoV in 2013. In 2019, cases of pneumonia with unknown etiology started to appear in Wuhan, China. Following that, on 7th January 2020; a new type of corona virus was isolated in China.This virus was previously known as 2019- Novel corona virus, which was renamed as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1]

In March, 2020, Government of India implemented a national lockdown which was extended till May 2020. [2] Cases continued to increase till September 2020; the control measures were implemented which effectively helped in reduction of the transmission. After the peak of first wave in September 2020, incidence started to decline steadily to less than 10,000 daily new case and 150 daily deaths in February 2021. [2] India surpassed 1 million active cases, and by April 2021, India became the second country with maximum COVID-19 cases worldwide. [3] It became necessary to assess patients so

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that they can be provided with better treatment and outcomes. Elevated level of C-reactive protein (CRP) has been found helpful in assessing to assist in triage, diagnostic and prognostication of many infections, including COVID-19 as well. Elevation in level of CRP in early stages in non severe COVID positive patients can help in predicting disease progression and to provide timely treatment to avoid associated mortality and morbidity. [4]

Material and Methods

This retrospective study was conducted after institutional ethical committee approval at tertiary care teaching hospital, during 2020 to 2023. Informed consent was taken from the patients and specimens for COVID-19 testing and C - Reactive Protein level estimation was collected from the them and received in the VRDL laboratory and biochemistry laboratory. A detailed clinical history was taken including the age, gender, travel, immune deficiencies, malnutrition and co-morbid conditions.

Sample size: 1000 patient samples

Inclusion criteria: Patient samples tested positive with COVID-19 RT-PCR.

Exclusion criteria: Patient samples tested negative with COVID-19 RT-PCR.

Collection of the sample: Samples were collected from the patients with influenza like illness. For rRT-PCR, synthetic fiber swabs were used and for CRP estimation, serum collection was done in red vacutte.

Testing procedure for SARS-CoV-2 rRT-PCR: Swab samples collected for COVID-19 were subjected to real time RT-PCR testing. At first, aliquoting was done followed by RNA extraction using Spin column based solid phase extraction method. Real time RT-PCR was done using Meril one step RT-PCR kit in ABI 7500 thermal cycler. For analysis of results, first, amplification curve of internal control ROX channel was analyzed (for RNaseP as an internal control); those samples with Ct value $\leq$ 35 were considered tested valid. In these samples, those with typical S-type (sigmoidal) amplification curve detected by FAM (for ORF gene) and HEX (for N gene) channel, with Ct value $\leq$ 35, were considered as positive for COVID-19. In samples where Ct value was more than 35 in FAM and HEX channel were considered as negative for COVID-19 virus, this was followed according to the kit standards.

C - Reactive protein estimation: Testing of serum samples for CRP estimation was done using MULTIGENT CRP Vario kit (Latex immunoassay) in ARCHITECT System, which was based on immunoturbidimetric principle.

Results

From 1000 COVID-19 positive patient samples included in the study, the mean age observed was 54.45 ± 16.43 years with a range of 0 to 98 years. Out of 1000 collected patient samples, 68.1% (n=681) patients were males and 31.9% (n=319) were female patients. [Table-1] [Figure-1]

Table : 1 Demographics and clinical summary

Results	***n=1000***
1. Age (Years)	54.45±16.43 years (**Range**: 0-98 years)
2. Gender	
Male	68.1% (n=681)
Female	31.9% (n=319)
3. No. of co-morbid patients	n=403/1000
4. CRP value	
Mild to moderate (0-100 mg/L)	67.8% (n=678)
Severe(>100 mg/L)	32.2% (n=322)
5. Mean CRP level	77.4 ± 79.6 mg/L

As shown in the table-1, From 1000 COVID-19 positive cases, CRP level was estimated from 0-100 mg/L in 67.8% (n=678) of cases and in 32.2% (n=322) cases, it was above severe level (>100 mg/L).

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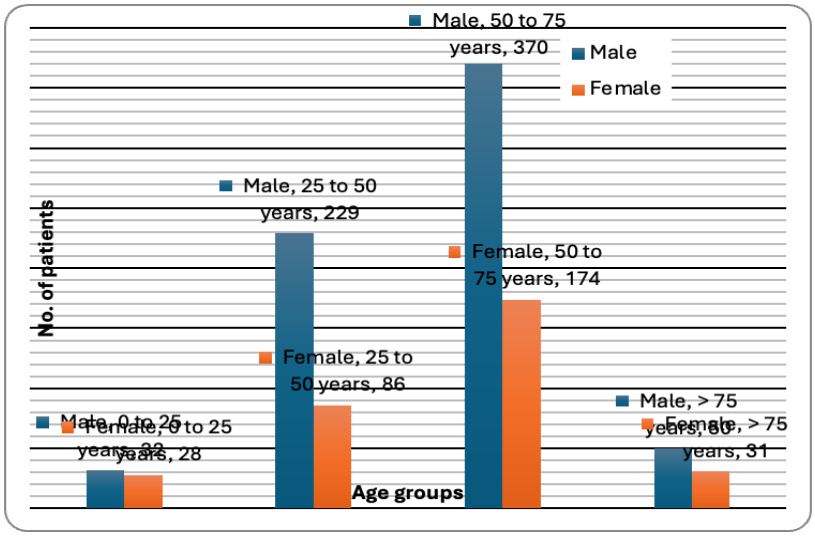

Figure-1 Demographic characteristics (Age wise)

Out of 1000 positive patients, 40.3% (n=403) patients were with severe pneumonia, ARDS and with co-morbidities such as obesity, hypertension, elderly age and chronic kidney diseases, these patients were considered as severe and other 59.7% (n=597) patients, which were considered as non-severe. [Table-2]

Table-2 Number of severe patients

Wards	No. of patients with co-morbidities	Median CRP level (185 mg/L)
ICU	47	12
Triage	139	81
COVID Positive Ward	217	134
Total	403	227

Receiver Operating Characteristic (ROC) analysis showed AUC value of 0.813 (95% CI: 0.787-0.840, p<0.001), sensitivity of 76.9%, specificity of 71% and cut-off value of CRP for severity was 52.2 mg/L. [Figure-2] [Table-3]

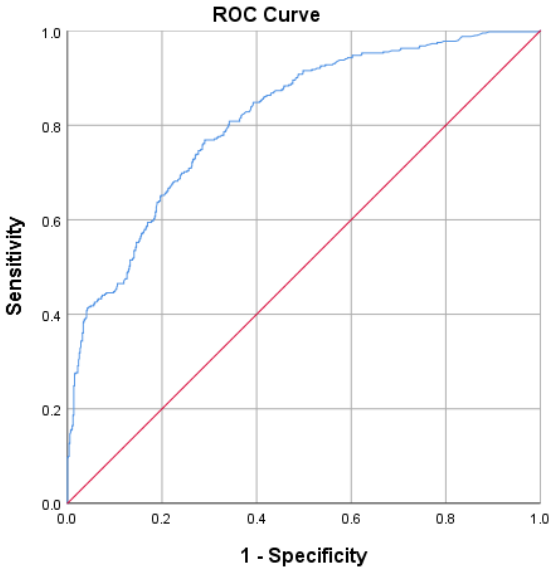

Figure-2 ROC analysis

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Table-3 Assessment of ROC

Assessment				
Variables	**AUC**	**P-value**	**Specificity**	**Sensitivity**
CRP	0.813	0.001	76.9%	71%

From these severe patients, 56.3% (n=227/403) showed median CRP level of 185 mg/L (IQR: 146 - 224 mg/L). From them, n=112/227 patients suffered a fatal outcome and could not survive, where CRP level tested was elevated above 190 mg/L.

Table-4 Comparison of mean CRP level

	Present study	Jacob Lentner et al[5]	Chen et al[6]
CRP level(mean ± SD)	77.4 ± 79.6 mg/L	78.7 ± 85.5 mg/L	51.4 ± 41.8 mg/L

Table: 5 ROC analysis

	AUC	**P-value**	**Cut-off CRP level** (mg/L)
Present study	0.813	<0.001	52.2
Fang Liu et al[8]	0.858	<0.001	41.8

Discussion

In this study, mean CRP level observed was 77.4 ± 79.6 mg/L, compared to the study of Jacob Lentner et al on COVID-19 outcomes, mean CRP level was 78.7 ± 85.5 mg/L and in the study of Chen et al on positive association of CRP level in severe COVID patients, mean CRP level observed was 51.4 ± 41.8 mg/L. [5, 6] [Table-4]

It was observed that among the patients admitted to ICU and positive wards with Severe Acute Respiratory Illness (SARI), ARDS, severe pneumonia and co-morbidities such as hypertension, obesity were 40.3% (n=403), cut off value of CRP in these severe patients observed was 52.2 mg/L (AUC=0.813, p-value<0.001). In another similar study of Fang Liu et al, where CRP along with other inflammatory markers were studied in mild and severe group, cut off CRP value in severe patients was 41.8 mg/L (AUC= 0.858, p value<0.001) [7] [Table-5]

From those severe and high-risk patients, 27.7% (n=112/403) patients could not survive and progressed to death, where cut off (Median) level of CRP observed was 185 mg/L (IQR: 146 - 224 mg/L), with highest measured CRP level of 318 mg/L. In the study of Varathrajan et al, similar outcomes were found; with increase in disease severity, CRP level was increasing significantly. In their study, 272 patients enrolled into study, 10.29% (28) died who were with co-morbidities and severe disease progression of COVID with CRP level cut off was 488 mg/L. In the retrospective study of Abdullah et al, 88 patients were included in the study, observed number of deceased patients were 22.8% with an average CRP value observed of 137.79 mg/L. This suggested that CRP level were correlated with increase in severity of COVID-19 and also as a predictor of fatal outcomes. [8, 9]

Conclusion

The findings of this study were comparable to those of previous studies, which reported role of acute phase biomarkers like CRP in infections. Acute phase reactants were found to be elevated, which is associated with increasing severity of the COVID. CRP could be used as independent marker to predict progression of COVID-19 and helps in assessing an increase in its severity, which ultimately can help in prediction of requirement of monitoring and supervision and providing treatment to this patients and also avoiding fatal outcomes. However, in our study, we included only C- reactive protein as biomarker, inclusion of other biomarkers such as interleukin-6, D-dimer or neutrophil to lymphocyte ratio could be added to provide better study results.

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