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Original Research Article

A STUDY OF CORRELATION OF FEVER PATTERNS AND C REACTIVE PROTEIN AND ITS OUTCOME IN COVID-19 PATIENTS AT TERTIARY CARE CENTER

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ABSTRACT

Background: Elevated C-reactive protein levels, which are regulated by IL-6, are linked to COVID-19 severity, and serve as a marker for inflammation, severe complications, and organ dysfunction. This study aimed to explore the level of CRP in the context of COVID-19 pathogenesis and assess how CRP levels change with disease severity.

Material and Methods: This prospective observational study included 100 patients with COVID-19 admitted to the isolation ward at GVMCH between February 2021 and January 2020. Patients were categorised based on fever duration prolonged fever (>7 days), saddleback fever, and fever lasting <7 days. Blood samples were collected, and RTPCR-confirmed COVID-19 patients from the isolation ward underwent necessary laboratory investigations.

Results: Approximately 58% of the patients were smokers and 26% were alcoholics, with common comorbidities including diabetes (46%) and hypertension (58%), while fever (84%) and headache (64%) were the predominant clinical features. Approximately 16 (16%) patients had prolonged fever, 12 (12%) had saddleback fever, and 72 (72%) had fever for < 7 days. There were significant differences in vital signs between the patients with fever ($p<0.01$). The prolonged fever group had significantly higher levels of CRP and LDH than the other groups ($p=0.01$). Additionally, the prolonged fever group exhibited significantly more consolidation ($p=0.01$). The prolonged fever group also had more cases of hypoxia and ICU admissions than the other groups, with significant differences observed ($p=0.01$, $p=0.05$).

Conclusion: Patients with COVID-19 and prolonged fever showed higher rates of hypoxia and inflammatory responses than those with saddleback fever, distinct cytokine profiles, and prognostic implications for optimizing hospital resource allocation in increasing cases.

Keywords: COVID-19, C-reactive protein, Fever, Inflammation, Cytokine storm.

INTRODUCTION

The new variant of coronavirus pneumonia (COVID-19) is a health emergency due to its higher rate of infectiousness1 and high case fatality rate in critically ill patients.[1] COVID-19's physiological and pathological processes are still under exploration, with CT scan imaging playing a crucial role in assessing disease severity.[2] C-reactive protein (CRP) levels can be a sensitive indicator for early pneumonia diagnosis, with higher CRP levels associated with severe cases.[3] We also assessed the correlation between levels of CRP, lung lesions, and disease severity to facilitate reference for clinical treatment.

Structural analysis of the virus has identified key binding regions, mutations, and host-specific proteins, such as TMPRSS2 and ACE2, which facilitate viral entry.[4] At the same time, epigenetic studies suggest that histone modification, DNA methylation, and ACE2 gene methylation may contribute to host tissue variability.[5] NAD-dependent histone deacetylase Sirtuin1 (SIRT1), will also regulate ACE2 in cell energy stress, which was upregulated in the lung tissue of severe new COVID-19 pneumonia patients.[6] Cytokine release syndrome (CRS), or "cytokine storm," is a critical condition in severe COVID-19 patients, characterized by the excessive secretion of chemokines and proinflammatory cytokines, contributing to multiple organ dysfunction and poor prognosis.[7]

C-reactive protein (CRP) is an acute-phase protein primarily regulated by cytokines such as IL-6 and IL-1β, and its transcription involves STAT3, NF-κB, and C/EBP. It plays a role in immune response by recognizing pathogen-associated molecular patterns, with limited extrahepatic synthesis significance.[8] CRP functions through mechanisms like immunoglobulins, such as promoting bacterial capsule swelling, agglutination, complement binding, phagocytosis, and the formation of complexes with polycations and polyanions.[9]

Of note, recent studies indicated that COVID-19-infected patients presented increased CRP levels and high levels of CRP were closely associated with a more severe variety of COVID-19, where age was considered the main risk factor for this poor outcome.[10] COVID-19 has been linked to stroke, CVD, T2DM, and sepsis, with CRP levels playing a critical role in these conditions. This review highlights the significance of CRP levels in COVID-19 and viral infections, emphasizing its predictive value for severe complications and organ dysfunction.

Recent studies have shown a positive correlation between C-reactive protein (CRP) levels and infection severity. CRP, produced by hepatocytes and stimulated by inflammatory mediators such as IL-6, is also associated with chronic conditions such as cardiovascular diseases and Type II diabetes mellitus.[11] Also, the early expansion of plasma CRP levels has been shown to elevate the likelihood of developing plasma leakage. Hence, CRP values could early predict COVID-19-associated severe pneumonia infections.[12] In this regard, although there are blood markers that appear to be linked with the degree of mortality and severity, the CRP level was sharply increased in severely SARS-CoV-2 infected patients.[13] The pathological, physiological, and diagnostic methods of COVID-19 are in the fact of finding stage.[14] Recent studies show a positive correlation between C-reactive protein (CRP) levels and the severity of infections. CRP, which is synthesized by hepatocytes, is stimulated by inflammatory mediators, such as IL-6. In addition to its role in acute inflammation, CRP is also associated with chronic conditions such as cardiovascular diseases and Type II diabetes mellitus.

Aim

This study aimed to explore the level of CRP in the context of COVID-19 pathogenesis and assess how CRP levels change with disease severity.

MATERIALS AND METHODS

This prospective observational study included 100 patients with COVID-19 who were admitted to the isolation ward in the Department of Medicine at GVMCH between February 2021 and January 2020. This study was approved by the Institutional Ethics Committee before initiation, and informed consent was obtained from all patients.

Inclusion Criteria

Patients of both sexes aged between 18 and 70 years who tested positive for covid 19 using RT-PCR were included.

Exclusion Criteria

Patients with a history of leukaemia, malignancy, autoimmune disorders on treatment, immunosuppressant therapy, and chronic infections, such as chronic hepatitis, tuberculosis, and HIV, were excluded.

Methods

Patients who were found to be RTPCR COVID-19 were enrolled. Patients were categorised based on fever duration, prolonged fever (>7 days), saddleback fever, and fever lasting < 7 days using convenience random sampling. Blood samples were collected for laboratory investigations. Patients were selected from the isolation ward and necessary laboratory investigations were performed.

Statistical Analysis

Data are presented as mean, standard deviation, frequency, and percentage. Continuous variables were compared using an independent-sample t-test. Categorical variables were compared using Pearson's chi-squared test. Significance was defined as P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0 (IBM-SPSS Corp., Armonk, NY, USA).

RESULTS

Table 1: Demographic details

		Frequency (%)
Age in years	< 20	6 (6%)
	21-40	14 (14%)

	41-60	24 (24%)
	> 60	56 (56%)
	Mean ± S. D	62.28 ± 1.86
Gender	Male	74 (74%)
	Female	26 (26%)
BMI (kgs)	< 18.5	2 (2%)
	18.5-22.99	18 (18%)
	23.0-24.99	30 (30%)
	≥ 25.0	50 (50%)
	Mean ± S. D	26.33 ± 3.42

Most patients in the > 60 years age group were 56 (56%). Approximately 24 (24%) were in the age group of 41–60 years. Approximately 14 (14%) were in the age group of 21-40 years. Only 6 (6%) patients were aged < 20 years. The mean age group was 62.28 ± 1.86. Approximately 74 (74%) patients were males and 26 (26%) were females. Most patients 50 (50%) were obese, 30 (30%) were overweight, and 18 (18%) had normal BMI. The mean BMI was 26.33 ± 3.42. [Table 1]

Table 2: Risk Factors, comorbidities, clinical features, and fever patterns

		Frequency (%)
Risk factors	Smoking	58 (58%)
	Alcoholism	26 (26%)
Comorbidities	Diabetes mellitus	46 (46%)
	Hypertension	58 (58%)
	Dyslipidemia	26 (26%)
	Cardiovascular disease	18 (18%)
Clinical features	Fever	84 (84%)
	Cough	52 (52%)
	Arthralgia	48 (48%)
	Headache	64 (64%)
	GIT symptoms	24 (24%)
Pattern of fever	Prolonged (n=16)	16 (16%)
	Saddleback (n=12)	12 (12%)
	Fever < 7 days (72)	72 (72%)

Approximately 58 (58%) were smokers and 26 (26%) were alcoholics. Regarding comorbidities, 46 (46%) patients had diabetes mellitus, 58 (58%) had hypertension, 26 (26%) had dyslipidaemia, and 18 (18%) had cardiovascular disease. Among the clinical features, 84 (84%) had fever, 52 (52%) had cough, 48 (48%) had arthralgia, 64 (64%) had headache, and 24 (24%) had GIT symptoms. Approximately 16 (16%) patients had prolonged fever, 12 (12%) had saddleback fever, and 72 (72%) had fever for < 7 days. [Table 2]

Table 3: Comparison of clinical, haematological, and radiological features of fever

		Fever (Mean)		**P value**
		Prolonged	**Others**	
Vital signs	Pulse rate	98	84	< 0.01
	Temperature	38.8	37.3	< 0.01
	Systolic BP (mmHg)	110	120	< 0.01
	Diastolic BP (mmHg)	66	76	< 0.01
	RR	22	19	< 0.01
	SPO2	96	98	< 0.01
Blood parameters	WBC (10^9/L)	4.8	4.6	0.54
	Hb (g/dl)	14.3	14.2	0.64
	Neutrophil (10^9/L)	2.81	2.82	0.97
	Lymphocyte (10^9/L)	1.02	1.45	0.86
	Platelet count(10^9/L)	164	211	0.03
	CRP (mg/l)	16	3.2	0.01
	LDH (u/l)	526	382	0.01
Radiological signs	Consolidation	8	24	0.01
	Progression on chest X-ray	12	Nil	NA
Outcome	Hypoxia	5	1	0.01
	ICU admission	2	1	0.05
	Mechanical ventilation	1	0	NA
	Death	0	0	NA

There were significant differences in vital signs between the patients with fever (p<0.01). The prolonged fever group had significantly higher levels of CRP and LDH than the other groups (p=0.01). Additionally, the prolonged fever group exhibited significantly more consolidation (p=0.01). The prolonged fever group also had more cases of hypoxia and ICU admissions compared to the other

groups, with significant differences observed (p=0.01, p=0.05). [Table 3]

DISCUSSION

In our study, most patients (56%) were aged >60 years old. About 24% were aged 41–60 years, 14% were aged 21–40 years, and only 6% were aged <20 years. The mean age was 62.28 ± 1.86 years. Approximately 74% of the patients were male, and 26% were female. Most patients (50%) were obese, 30% were overweight, and 18% had normal BMI. The mean BMI was 26.33 ± 3.42. Among the participants, 58% were smokers and 26% were alcoholics. Regarding comorbidities, 46% had diabetes mellitus, 58% had hypertension, 26% had dyslipidaemia, and 18% had cardiovascular disease. Clinically, 84% had a fever, 52% had a cough, 48% had arthralgia, 64% had headache, and 24% had gastrointestinal symptoms.

Regarding fever duration, 16% had prolonged fever, 12% had a saddleback fever, and 72% had a fever lasting < 7 days. Significant differences in vital signs were observed between groups (p<0.01). CRP and LDH levels were significantly higher in the prolonged fever group than in the other groups (p=0.01). Additionally, the prolonged fever group exhibited significantly more cases of consolidation (p=0.01). This group also had higher rates of hypoxia and ICU admission, with significant differences noted (p=0.01, p=0.05, respectively).

In a study by Wu et al., a rise in CRP and LDH was seen in patients with prolonged fever, which is known to be associated with adverse prognostic factors in COVID-19, and Shi et al. demonstrated a statistically significant association between cardiac injury and mortality in patients with COVID-19. Cardiac injury, a common complication (19.7%), is associated with an unexpectedly high risk of mortality during hospitalization.[15,16] This suggests that close monitoring of deterioration should be instituted in patients with prolonged fever.

In our study, patients with other fevers who remained well could be monitored in the community, whereas patients who had a fever for >7 days should be admitted for closer monitoring. Fridkin et al. reported that patients in the ICU are at a higher risk of nosocomial infections; therefore, due diligence should be performed to exclude other causes of fever.[17] Physicians may consider stopping antimicrobials in stable patients with unyielding investigations while optimising COVID-19 patient placement in isolation facilities to reserve hospital beds for severe cases. Teleconferencing and self-recorded temperature monitoring can help triage COVID-19 patients in isolation facilities, as fever is an easily detectable indicator of potential disease severity.

Wang et al. reported that CRP levels and diameter of the largest lung lesion in the moderate group were higher than those in the mild group (p<0.05), those in the severe group were higher than those in the moderate group (p<0.05), and those in the critical group were higher than those in the severe group were significant differences (p<0.05). CRP levels positively correlated with the diameter of the lung lesion and severe presentation (correlation coefficient = 0.873, 0.734, p < 0.001).[12] Sahu et al. found that a meta-analysis demonstrated a significant role of CRP in COVID-19 infection outcomes (p=0.000).18 Lorè et al. study, the fifty-three potential biomarkers, and the classification tree analysis selected CXCL10 at hospital admission, in combination with NLR and time from onset, as the best predictor of ICU transfer AUC (95% CI) = 0.8374 (0.6233–0.8435), whereas it was selected alone to predict death AUC (95% CI) = 0.7334 (0.7547–0.9201). CXCL10 concentration decreased in COVID-19 survivors after healing and discharge from the hospital.[19]

Clinical monitoring and appropriate treatment strategies are essential to improve the case fatality rate. CT scan imaging plays an important role in assessing the disease.[2] Other sensitive indicators that can reflect lung lesion changes and disease severity must be explored. C-reactive protein (CRP) values can be used in the early diagnosis of pneumonia, and the patients presenting with severe pneumonia had higher CRP levels.[3]

CONCLUSION

In conclusion, we reported the prevalence, risk factors, cytokine profiles, and outcomes of patients with COVID-19 who had saddleback or prolonged fever. Patients with prolonged fever were more likely to develop hypoxia and had a more pronounced inflammatory response than those in the saddleback fever group, which is also reflected in the different cytokine profiles between the two groups. The different prognoses for these two groups of patients have implications for the distribution of increasingly burdened hospital resources, given the exponential rise in cases worldwide.

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