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Fever Pattern — A Prognostic Factor for Adverse Outcome in Covid-19

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Abstract

It is our current understanding that the COVID-19 pandemic represents one of the most critical problems humanity has encountered in the 20th century. Currently, there is enormous ongoing research to understand the disease dynamics. Most patients only have mild symptoms and relevant proportional develops severe disease progression with increasing hypoxia up to acute respiratory distress syndrome. We conducted a retrospective data analysis of cases of COVID-19 diagnosed during the second spike of the COVID-19 pandemic in Delhi, the national capital of India, to identify clinical variables that allowed the prediction of the patient with a high risk of respiratory failure and need for mechanical ventilation. This study consists of 300 COVID-19 patients who had consulted at the clinic. Fever was defined as the temperature of 38degreeC(100.4F). Prolonged fever (more than 5 days) and saddleback fever (recurrence of fever, lasting less than 24 hours, after defervescence beyond day 5 of illness) were defined.

Haematological and radiological data were determined. The adverse outcomes were hypoxia, intensive care unit (ICU) admission, mechanical ventilation, and mortality. 38% (116/300) cases had prolonged fever and 25.6% (77/300) patients had a saddleback fever. Both prolonged (36.2% versus 0.0%) and saddleback fever (19.4% versus 0.0%) were associated with hypoxia compared with control cases with prolonged Fever had also increased CRP (100%) lymphocytopenia (78%) and increased LDH (100%). Cases with prolonged fever were also more likely to require ICU admission compared with controls (9.4% versus 0.0%).

Keywords: COVID-19, Fever, Hypoxia, Prolonged, Saddleback

INTRODUCTION

It is our current understanding that the COVID-19 pandemic represents one of the most critical problems humanity has encountered in the 20th century. As of 15th July 2021, more than a 188.6million confirmed cases of COVID-19 have been reported worldwide and more than 4.06 million deaths have been reported by the WHO [1]. In India also confirmed cases reached more than 30.98 million and death cases crossed to 0.41 million till date[1].

The recent second Coronavirus spike in Delhi, the national capital of India has reported 768,968 (7.68lac) infections and 13,936 deaths in the last 3 months from April 2021 to June 2021[2]. During the second spike of Coronavirus health services providers faced an enormous burden leading to the majority of COVID-19 patients being stranded at home only, where they did not have adequate surveillance and laboratory backup, culminating in adverse outcomes of COVID-19. With this exhilarating news, we need to understand how the clinical parameters are acting in this new wave of the epidemic, which may help the administration make proper health interventions in

[1] From https://www.mohfw.gov.in/

[2] https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Delhi

future. During an outbreak effective screening tool is essential to identify the patients at risk for severe disease. Determination of factors that predict initial and subsequent need for hospitalisation, ICU services is critical for resources, planning and allocation. Many Scholars found that changes in blood parameters like CRP, D-dimer, LDH combined with patients age and medical complications had distinct Instructive values for critical COVID-19 patients prognosis [2], [3], [4]. So there is a need to identify clinical and laboratory predictors of the progression to a fatal form of the disease. Fever and cough are common symptoms of COVID-19. Only a few studies have evaluated fever patterns as an association with the severity of COVID-19 [5], [6], [7], [8]. Deborha et al in their study of 142 admitted patients found prolonged fever is a prognostic factor in covid-19, [5] but this study had included only a small number of cases that too admitted in hospital, so we conducted a retrospective study of 300 patients who consulted at a clinic in Delhi.

MATERIAL AND METHOD

This retrospective cohort study was conducted based on the result obtained from 300 patients with confirmed COVID-19, who consulted at the clinic from 1st April to 30th June 2021. In this study we analysed the medical records (electronic), demographic and comorbidity data, laboratory and radiology results were obtained. In this study of 300 coronavirus confirmed cases were divided into 3 clusters of patients. Patients with fever less than 5 days, saddleback fever and fever more than 5 days. Fever has been defined as a temperature of 100.4 degrees Fahrenheit (38 degrees C) or higher. Duration of fever was calculated from the date of first symptom onset to the date of defervescence (defined as temperature less than 99.5 degrees F (37.5 degrees C) for at least 24 hours.). Cases with saddleback fever were defined as patients with recurrence of fever lasting less than 24 hours after defervescence, beyond day 5 of illness. Cases with prolonged fever were defined as patients with fever lasting more than 5 days. Cases without prolonged fever or saddleback fever were included as a cohort control. Non-communicable diseases like cardiovascular disease, hypertension, CAD, diabetes mellitus and other immunocompromised states, chronic lung/ kidney /liver disease, cerebrovascular disease and obesity were considered as comorbidity.

Hypoxia was defined as oxygen saturation less than 93%. Outcomes of interest were hypoxia (less than 93%), hospital admission, need for ICU admission and mechanical ventilation and mortality. Data of patients who were hospitalised were analysed by their discharge summary.

RESULTS

Results of this study included 300 Coronavirus infected patients with a median age of 46.1 (32 -75) years. The majority of patients were male (204/309) accompanied by 32% (96/300) females. 38% (116/300) of cases had prolonged fever and another 25.6% (77/300) patients had a saddleback fever. 32.3% (107/ 300) of patients who had a fever for less than 5 days were treated as cohort control (Table 1).

35% (106/300) of patients had comorbidities of which 46.2% (49/106) patients were of more than 60 years of age. 41.3% (48 /116) patients with comorbidities had prolonged fever and 41% (32/77) comorbid patients had a saddleback fever.

24% (26/107) patients were having comorbidity in the control group. During this period of the second spike of COVID-19 many patients could not get their haematological and radiological tests being done.

In patients having saddleback fever patterns, fever recovered at a median of 9 days (8-11) after symptom's onset. In 5 patients there was a recurrence of fever after defervescence which lasted more than 24 hours, out of these 5 patients, 3 patients developed hypoxemia and were admitted and one patient expired. Leucopenia (22.4%) and lymphocytopenia (38.6%) along with thrombocytopenia (52.8%) was noted in patients with saddleback fever. CRP was increased (median 15.8) in all patients with saddleback fever (Table 2).

Cases with prolonged fever (116/300) had a median duration of fever lasting 10 days (8-14). Prolonged fever was also associated with leucopenia (48.2%), lymphocytopenia (64.6%) and thrombocytopenia (72.4%). CRP was increased (60.6 median) in all patients (Table 2).

11 patients had Pneumonitis in the control group on X-ray/ CT scan chest. None of them had hypoxia. 43 patients with saddleback fever had pneumonitis on X-

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ray/ CT scan chest (52 patients got X-ray/ CT scan chest being done). 100% (90/90) patients with prolonged fever had pneumonitis on the X-Ray chest /CT Scan chest (Fig 1).

15 patients with saddleback fever (15/77) had hypoxia whereas 42 patients with prolonged fever (42/116) had developed hypoxia (Oxygen saturation less than 93%). Out of this 7 patients with saddleback (7/15) and 28 patients with prolonged fever (28/42) were admitted, rest of the patients with hypoxia in both groups had supplemental oxygen therapy at home and recovered. 2 patients with saddleback fever (2/7) and 11 patients with prolonged fever (11/28) required ICU admission. Mechanical ventilation was needed in 1 patient with saddleback fever (1/2) and 5 patients with prolonged fever (5/11). All patients who needed mechanical ventilation expired (Table 3).

Cases with prolonged fever were more likely to have hypoxia (36.2% vs 0%), hospital admission (24.23% vs 0%) and ICU admission (9.4% vs 0%) and mechanical ventilation (4.3% vs 0%) compared with cases in control group. Saddleback fever was also associated with hypoxia (19.4% vs 0%), hospital admission (9.09% vs 0%), ICU admission (2.5% vs 0.0%) compared with those in the control group. 5 patients with prolonged fever and one with saddleback fever died from acute respiratory distress syndrome.

DISCUSSION

The number of patients with COVID-19 is increasing globally and COVID-19 related fatality is also increasing. COVID19 is a new threat for the population and till date, no specific treatment has been recommended by WHO, CDC [9] and so treatment options need to be evaluated. Early monitoring of the key indicators is an important basis to get guide treatment strategies and early assessment of the severity of patients condition is of great value. Fever and cough are the most common symptom in COVID-19 patients. The initial presentation of the fever in COVID-19 in the first week, during the viral phase of the illness, is likely a manifestation of the body's immune response to the viral replication to augment immunity. However, if the viral replication does not resolve in due course, the disease process is complicated by the viral triggered state of the dysregulated inflammation described as cytokin storm or secondary haemophagolymphocytosis, heralded by unremitting fever. In such cases where extreme inflammation sets in, fever can be counterproductive. Fever may promote further inflammation and further immune activation may not be beneficial at this stage. The role of immunity in COVID-19 in the early and later phase of the illness can be gauzed from the recent trial [10]. Few studies have considered high temperature to be related to the progression of the COVID-19 [5], [6], [7], [8]. In this retrospective study, COVID-19 patients with prolonged fever showed a more pronounced inflammatory response and were more likely to require ICU admission than cases with saddleback fever or fever for less than 5 days. Prolonged fever beyond 5 days from onset of illness can identify patients who may be at risk of adverse outcomes from COVID-19. Patients with saddleback fever appear to have a good outcome. Based on this study we propose patients with saddleback fever who remain well can be monitored in the community while patients who were having fever for more than 5 days should be admitted for closure monitoring.

LIMITATIONS

The limitation of our study was retrospective design. Detailed biomarkers of COVID-19 could not be evaluated because of the burden on Laboratory work during the second spike of COVID-19 cases in Delhi. Because of the retrospective design of the study, there might be a concern of bias in the sensitivity of the patients in the diagnosis of hypoxia in home quarantine patients. Another limitation is the onset of fever was dependent upon self-response by patients so over or under respond may be there. Many patients did not get admitted to the hospital, took antipyertic round the clock so that actual temperature was affected. Detailed medical records of five cases who expired was not available.

CONCLUSION

Prolonged fever in COVID-19 patients predicted the development of hypoxia, the requirement of oxygen therapy with excellent sensitivity and specificity. Further studies are needed to evaluate the real benefits of observation of the pattern of fever and its use as a predictive factor of severe disease.

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TABLES AND FIGURES

Table 1: Sample profile (Sample size – 300)

Gender
- Male - 204
- Female - 96

Age Group (median - 46.4 years)
- <60 - 206
- >60 - 94

Comorbidities
- <60 age group: 57
- >60 age group: 49
- Total: 106

Table 2: Median values of main blood test measures

Blood test	Saddleback	Prolonged fever
Hb (g/dL)	12.8 (10.6 – 14.2)	12.6 (10.6 – 13.6)
TLC (10^9/L)	4.6 (3.2 – 7.0)	4.4 (3.1 – 6.5)
Platlet count (10^9/L)	1.85 (1.1 – 3.5)	1.64 (1.02 – 3.6)
Neutrophil (10^9/L)	2.82 (1.9 – 3.4)	3.01 (2.01 – 3.2)
Lymphocyte (10^9/L)	1.224 (0.94 – 1.48)	1.032 (0.9 – 1.3)
AST (SGOT) – U/L	34 (20 – 42)	46 (30 – 56)
ALT (SGPT) – U/L	46 (22 – 55)	64 (40 – 86)
CRP (mg/L)	15.8	60.6
LDH – U/L	457 (382 – 510)	648 (536 – 732)
IL6 – pg/L	22	52

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	(5 – 40)	(12 – 88)
Oxygen saturation (%)	96 (92 – 97)	95 (90 – 97)

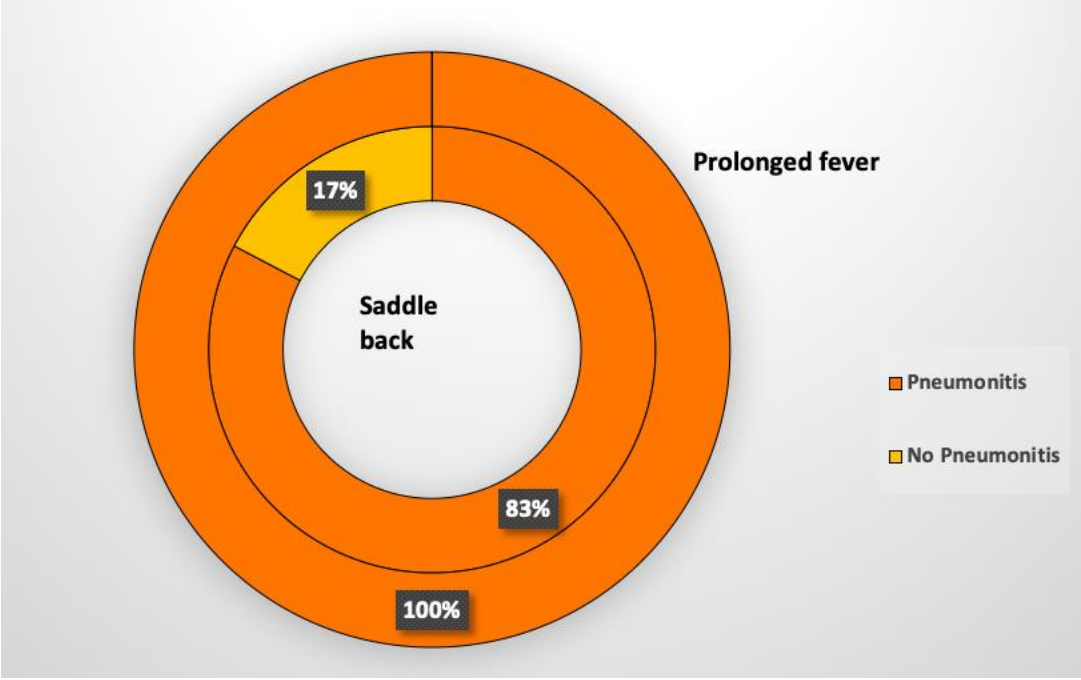
Note: Values in parentheses represent range.

Table 3: Number of patients with adverse outcomes

Adverse Outcome	Saddleback	Prolonged fever
Hypoxia (<93%)	15 (4)	42 (16)
Hospitalization	7 (4)	28 (16)
ICU	2 (2)	11 (7)
Mechanical Ventilation	1 (1)	5 (3)
Death	1 (1)	5 (3)
Age groups	<60	3 (>60) 2 (<60)

Note: Number in parentheses represents number of patients with co-morbidities.

Fig 1: X-ray Chest/ CT scan Results



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