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High Level of on Admission CRP is Directly Associated with Increased Severity and Mortality in Patients with Covid-19

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ABSTRACT

Background: Many studies have been done to identify the clinical characteristics of covid infected patients. Study by Lawrence A Potempa et all has shown the association between CRP levels and disease severity in Covid-19 positive patients. Whether high levels of on admission C-Reactive Protein are associated with increased incidence of severity and mortality in COVID-19 patients remains to be investigated.

Methods and Materials: A Retrospective cohort study was conducted on 199 patients with COVID-19 infection who were admitted to SSG Hospital,Vadodara.The on admission Clinical and laboratory data was collected from Medical records and Statistics department of SSG hospital. The patients were classified into mild, moderate, severe and critical according to the Clinical management of COVID 19 by WHO.[21]

Results: Of 199 cases 52 were classified as severe cases and 18 as critical cases. The mean on admission CRP Levels of the severe group was significantly higher than that of mild group (69.95 vs 20.95, P = <0.0001). Patients with High level of on admission CRP (>50) were more likely to be admitted in ICU, Require supplemental oxygen and mechanical ventilation with increased average hospital stay. High levels of On admission CRP were also associated with increased in hospital mortality in Covid infected Patients.

Conclusion: High levels of on admission CRP are associated with increased incidence of severity and mortality among Covid-19 positive patients.

Keywords: COVID 19, CRP, INFLAMMATORY MARKERS.

INTRODUCTION

In December 2019 a new virus was reported in hospitalized patients in Wuhan, China.[()]The pathogen was identified as a novel Enveloped betaCorona Virus.[(2)] It was named as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), due to its phylogenetic similarity with SARS-CoV.[(3)] On January 30,2020 the WHO(World Health Organization) declared Corona virus Disease 2019 A Public health Emergency Of International Concern.[(4)] As of January 2021 there are more than 100 million reported cases of corona virus infection with more than 2 million deaths. In India Itself there were more than 10 million Covid-19 Positive cases, also resulting in more than 150000 deaths.[(5)]

An important aspect to highlight during the present crisis is the speed at which research studies have been developed, leading toward a better understanding of the epidemiology, clinical manifestations, risk factors, and transmission dynamics,[(6,7,8, 9)] as well as the identification of the etiological agent[(10,11)] including its genome, morphological structure, and molecules[(12,13,14)] its relationship with other corona

viruses[15] ,its entrance into the host cells by binding the Angiotensin II Converting Enzyme (ACE2)[10], its intracellular replication,[16] and the immune response of the infected individuals.[17,18,19,20]

In developing countries like India the resources available for critical disease management are limited.There have been many incidences where patients have lost their lives because of lack of availability of ICU beds. Limited resources with no standardized treatment are crucial problems. So it is of utmost importance to identify the risk factors early upon hospital admission so that appropriate resources may be diverted towards them.Early intervention is the key to accelerate recovery and shorten the course of the disease. Many studies indicate a strong co-relation between disease progression and various inflammatory markers. C reactive protein is widely used as a diagnostic marker of ongoing inflammation due to its easy availability. CRP values in normal healthy individual is less than 10ug/ml. Values between 10ug and 50ug indicate ongoing inflammation which can be either acute or chronic but the CRP levels above 100ug indicate fulminant inflammation and poor prognosis.[22] The objective of this study was to identify whether high levels of on admission C reactive protein are associated with increased incidence of severity and mortality in COVID-19 positive patients and whether it can be used efficiently as an diagnostic index of disease severity so that the use of health care resources can be prioritized for the appropriate patient.

METHODS

Study Design

This is a retrospective single centre study carried out on a sample of randomly selected COVID-19 positive patients treated at Sir Sayaji Rao Hospital, Vadodara.It is a tertiary health care centre with a separate building for COVID-19 positive patients.This study was approved by Institutional Ethical Committee of Sir Sayaji Rao Hospital, Vadodara.

The Severity classification of patients with Covid-19 infection was done according to the Clinical management of COVID-19 by WHO.[21] The condition on admission was considered Serious according to the following criteria :Adult with clinical signs of pneumonia plus one of the following: respiratory rate > 30 or SpO2< 90% on room air. Patients were considered Critical if they were diagnosed with ARDS, Sepsis,Septic Shock.Patients were treated according to the guidelines provided by ICMR, India.

Data Collection

Patients of more than 18 years of age with Covid-19 Positive result through RTPCR test done in microbiology laboratory of Sir Sayaji Rao Hospital or through the Rapid Antigen Kit approved by ICMR were included in the study.Pregnant females, patients on immunosuppresive medications, patients transferred into or out from other facilities were excluded from our study.

The data collected included demographic data, symptoms and signs, past medical history, radiological findings, on admission vitals, laboratory results from medical records and statistics department of Sir Sayaji Rao Hospital, Vadodara.The following data was also collected: total days of hospitalization, requirement of supplemental oxygen, requirement of mechanical ventilation,requirement of ICU admission throughout the treatment process and cause of death.Laboratory results included on admission complete blood count, renal function tests, liver function tests, inflammatory markers like CRP, D dimer, LDH, Ferritin, IL-6, Pro-calcitonin, Pro-BNP, HbA1c and random blood sugar. The laboratory data of some patients was missing because of absence of certain test types. The data which support these findings are available from Sir Sayaji Rao Hospital,Vadodara. Restrictions may apply to the availability of these data , which were used under license for this study. The data used in this study was anonymous, so the requirement of obtaining informed consent was waived.

Statistical Analysis

Descriptive statistics were presented as means ± S.D. for continuous variables and as percentages for categorical variables.Student's t-test was used to compare normally distributed continuous variables, whereas the Mann–Whitney U-test was applied for data not obeying a normal distribution, which was represented by the median (lower quartile, upper quartile). The non parametric Chi-square test was used to compare categorical variables. ANOVA was used to compare multiple categorical data.

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Multivariate logistic regression was used in the two models to obtain the odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs)between the tertiles of CRP and the incidence of severe cases of Covid 19.Model 1 was adjusted for age, C reactive Protein, Co-morbidities, Hypertension, Diabetes mellitus. Model 2 was adjusted for C reactive protein, D dimer, Lactate Dehydrogenase, Ferritin, Neutrophil-Lymphocyte ratio.Similarly Multivariate logistic regression was used in another two models to obtain the odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs)between the tertiles of CRP and the incidence of in-hospital mortality in cases of Covid 19.Model 3 was adjusted for age, C reactive Protein, Co-morbidities, Hypertension, Diabetes mellitus. Model 4 was adjusted for C reactive protein, D dimer, Lactate Dehydrogenase, Ferritin, Neutrophil-Lymphocyte ratio.The lowest tertile of CRP was used as the reference under each model to calculate the ORs and the corresponding 95% CIs. All data were analysed using MedCalc version 19.8.0.0. $P < 0.05$ was regarded as statistically significant in all statistical analyses.

RESULTS

Demographic and clinical characteristics

Of the 199 patients included in this study mean(standard deviation)age of the population was 53.22 years (+/-16.58) and of it 133 (67%) were men.Table 1 shows the demographics and clinical characteristics of the patients according to the severity.Of the 199 patients included in the study 67(33%)were classified on admission as mild,62 (31%) as moderate, 52 (26%) as severe and 18(9%) as critical. Patients in severe group were comparatively older than mild group (62.3 (13.25) vs 44.7 (15.2), P value <0.0001). No significant difference in proportion of women was found among both mild and severe group(28.8%). In both the groups majority of patients presented with fever. Compared with mild cases, severe cases were more likely to have shortness of breath (P value<0.0001). Mild cases mostly presented with fever and generalized body ache. Compared to mild group,patients in severe group were more likely to have co-morbidities like hypertension, diabetes mellitus, heart disease and obesity.Absolute WBC count was significantly elevated in the severe group than in the mild group (12070 vs 6459, P = <0.0001 and 4.3 vs. 3.1,P < 0.001, respectively), similarly the Neutrophil-Lymphocyte ratio was also significantly elevated in severe group than in mild group(6.08 vs 2.26, P Value <0.0001). No significant difference in haemoglobin and platelet count was found among both mild and severe group.Bio markers like D dimer(3781.47 vs 540.89, P= <0.0001), CRP (69.95 vs 20.95, P = <0.0001), Ferritin (571.33 vs 169.14, P= <0.0001) Lactate dehydrogenase (LDH)(1179.35 vs 505.01, P = <0.0001) were also significantly elevated in severe group as compared to the mild group. In severe group Creatinine (1.43 vs 1.04, P= 0.0002), Blood Urea Nitrogen (BUN) (55.71 vs 35.06, P=<0.0001),Alanine transaminase (ALT)(41.40 vs 28.72, P= 0.0029), Aspartate aminotransferase (AST) (62.34 vs 36.3, P=<0.0001) were also significantly elevated.

Of these 199 patients, 65(32.5%) were admitted in ICU, 113(56%) required supplemental oxygen at some point during their hospital stay, 58(29%) required mechanical ventilation with the in hospital mortality of 55(28%).

Table 2 shows the relationship of on admission CRP values with different grades of severity. The mean on Admission CRP values in the severe group are significantly higher than the mild group. Figure 1 shows that as the severity increases the mean CRP values also increase.

As shown in table 3 CRP was divided into tertiles with tertile 3 having CRP values more than 50 mg/dl. Factors such as on-admission SpO2, requirement of mechanical ventilation, requirement of supplemental O2, requirement of ICU admission and outcome were used as severity indicators. The mean on-admission SpO2 was significantly lower in patients of tertile 3 compared to patients in tertile 1(P <0.0001).The average duration of hospitalization of patients in tertile 3 was also significantly high(P <0.001). Patients in Tertile 3 were more likely to require supplemental oxygen (P < 0.0001) at some point during their hospital stay. They were also more likely to require mechanical ventilation (P< 0.0001) and subsequent ICU admission (P<0.0001) with significantly high in-hospital mortality (P<0.0001).

Multi variable logistic regression was used to analyse the correlation between CRP levels and the Incidence of severe Covid 19 Positive cases (Table 4). CRP was

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divided into tertiles. The lowest CRP level was used as the reference, and the categorical variables were analyzed. The unadjusted logistic regression analysis indicated that upper categorical levels had a statistically significant higher risk of severity than that of lower levels(Odd ratio= 9.79E).After adjustments for age,Co-morbidities, diabetes mellitus and hypertension, the highest tertile remained statistically significant (OR=7.23E).Further adjustments for other factors, including LDH,Ferritin, D-dimer, NLR showed that the highest level of relative risk (OR=23.6E) remained significant with higher CRP values.

DISCUSSION

This retrospective cohort study included 199 in hospital patients. We found that high levels of on admission C reactive protein are associated with increased disease severity and mortality in COVID-19 positive patients. High values of on admission CRP are associated with increased in hospital stay, increased ICU admission, requirement of supplemental oxygen and requirement of mechanical ventilation. High values of CRP are associated with increased in hospital mortality.

Study by Lawrence A Potempa et al [(22)] reported that there was substantial tissue involvement in patients with high level of CRP and that high CRP level is a diagnostic marker of severe inflammation. CRP levels reflect on the degree of tissue involvement and can help diagnose confounding complications. A study by Tan et all[(23)] all showed a direct association between CRP levels and CT grading in COVID positive patients. Patients with moderate and severe CT grading had higher CRP level as compared to patients with mild CT grading.Similarly the study of Lawrence A Potempa et all [(22)] also showed that at an early stage of COVID-19, CRP levels were positively correlated with lung lesions. C reactive protein levels could reflect disease severity and can be used as a key indicator for disease monitoring.

The severe group also showed other elevated bio markers for infection.Patients in severe group had high Neutrophil-lymphocyte ratio. A study (n = 61) recently reported increased incidence of severe illness with NLR ≥ 3.13.[(25)]Similarly another study reported that Patients with D- dimer levels ≥2.0 µg/mL had a higher incidence of mortality [(24)] which is also consistent with our findings.Similarly a study done by chang li et al (n=203) reported that elevated LDH was independently associated with increased disease severity and mortality in Covid-19 positive patients.[(26)] Our results also suggest similar trend.Recently a study conducted by zhin li et al found that higher serum Ferritin was an independent predictor of disease severity in patients with COVID-19.[(27).] In our study also, the on admission Ferritin levels were significantly elevated in severe group as compared to mild group. The future challenge is finding a way to combine all the bio markers so that effective screening test can be identified and applied for the early identification of patients who may have increased disease severity.

Our study has several advantages.In country like India where resources are limited,early identification of risk factors is vital to identify patients who may progress to severe disease. Early intervention is the key to accelerate recovery and shorten the course of the disease.On the basis of the current study, Covid-19 positive patients who are suffering from pneumonia and those with high level of on admission CRP(>50mg/dl) should be compulsorily admitted to a tertiary care hospital with respiratory monitoring and supportive care rather putting them into home isolation.Patients with on Admission CRP values of >12mg/dl should be admitted in an isolation centre for effective monitoring rather than home isolation. Patients with CRP levels <12mg/dl should be home isolated. This findings are important in the way that they will help identify patients early in the disease process and help reduce the mortality caused due to untimely or delayed intervention. This study will also help in prioritizing health care resources more effectively. This study also has some limitations: it was a small-sized,single-centre and retrospective study (a larger cohort would be better to eliminate potential bias), and for some patients,repeated measurement data were provided on the first day,the first data point was always used, resulting in potentially incomplete information on variations in intraday values.

CONCLUSION

C reactive protein can be used efficiently as an diagnostic index of disease severity and mortality early on in the disease process so that the use of health care resources can be prioritized for the appropriate patient.

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TABLES/FIGURES (.JPG)/GRAPHS (EXCEL)

TABLE 1:

PATIENT CHARACTERISTICS	**ALL PATIENTS N=199**	**MILD N=67**	**SEVERE N=52**	**P value**
AGE(years)	53.22+/-16.5	44.79+/-15.32	62.3+/-13.24	<0.0001
<=60	124 (62.31%)	55 (82%)	37 (71.15%)	
>60	75 (37.69%)	12 (18%)	15 (28.85%)	
GENDER				
Male	133 (66.84%)	45 (67.16%)	37 (71.15%)	
Female	66 (33.16%)	22 (32.84%)	15 (28.85%)	
SYMPTOMS				
Fever	126 (63%)	47 (70%)	33 (63.4%)	0.56
Breathlessness	91 (46%)	9 (13.4%)	45 (86.5%)	<0.0001
Cough	100 (50%)	29 (43.2%)	26 (50%)	0.61
Sore throat	6 (3%)	3 (4.5%)	2 (3.8%)	0.77
Nausea/Vomiting	13 (6.5%)	2 (2.95%)	3 (5.7%0	0.77
Diarrhoea	13 (6.5%)	2 (2.95%)	4 (7.6%)	0.45
Loss of Taste	4 (2%)	4 (5.9%)	0 (0%)	0.20
Weakness	38 (19%)	14 (20%)	7 (13.4%)	0.416
Abdominal pain	9 (4.5%)	2 (2.95%)	3 (5.7%)	0.72
Anorexia	12 (6%)	4 (5.9%)	1 (1.9%)	0.32
Bodyache	23 (11.5%)	15 (22.3%)	1 (1.9%)	0.002
Headache	8 (4%)	4 (5.9%)	2 (3.8%)	0.9
Others	13 (6.5%)	2 (2.95%)	4 (7.6%)	0.45
CO-MORBIDITIES				
Smoking	1 (0.5%)	0 (0%)	0	0.2
Hypertension	58 (29.1%)	12 (17.9%)	28 (53.8%)	0.001
Diabetes Mellitus	63 (31.65%)	12 (17.9%)	23 (44.23%)	0.0056

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Heart disease	8 (4%)	0 (0%)	4 (7.6%)	0.07
Tuberculosis	2 (1%)	1 (1.5%)	0	0.89
Obesity	3 (1.5%)	0	3 (5.76%)	0.16
Chronic Kidney Disease	2 (1%)	0	0	0.2
Chronic Liver Disease	1 (0.5%)	0	1 (1.92%)	0.89
Hypothyroidism	7 (3.5%)	3 (4.5%)	1 (1.92%)	0.79
Chronic Respiratory Disease	5 (2.5%)	0	1 (1.92%)	0.89
HIV	3 (1.5%)	0	1 (1.92%)	0.89
Others	11 (5.5%)	3 (4.5%)	2 (3.84%)	0.77
LABORATORY FINDINGS				
Hemoglobin(gm%)	12.1(2.33)	12.6 (10.82-14.52)	11.92(9.33-14.5	0.0691
WBC(/c mm)	9568.7(6713.6)	6459.25(4295.28-8623.22)	12070.9(4771.97-19368.93	<0.0001
Neutrophil/Lymphocyte Ratio	3.989(3.84)	2.26 (1.08-3.44)	6.08(1.45-10.71)	<0.0001
Platelets(/c mm)	2.23(1.06)	2.13 (1.34-2.92)	2.28 (1.09-3.47)	0.4265
Blood Urea(mg/dl)	47.37(29.9)	35.06 (22.43-47.69)	55.71(34.8-76.62)	<0.0001
Blood Creatinine(mg/dl)	1.35(1.17)	1.04 (0.8-1.28)	1.43 (0.65-2.21)	0.0002
SGOT(IU/L)	48.94(31.21)	36.3 (19.81-52.79)	62.34 (26.53-98.15)	<0.0001
SGPT(IU/L)	34.57 (26.54)	28.72 (11.82-45.62)	91.40(63.13-119.67)	0.0029
LDH(IU/L)	824.76 (505.52)	505.01 (306.12-703.9)	1179.35(823.17-1535.53)	<0.0001
D-Dimer(ng/ml)	1910.17 (3770.4)	540.89 (446.49-1528.27)	3781.47(1862.93-9425.87)	<0.0001
CRP(mg/dl)	47.27(54.77)	20.92 (14.8-56.54)	69.95(15.32-124.58)	<0.0001
Ferritin(ng/ml)	341.64 (390.830)	169.14 (19.58-357.86)	571.33(73.92-1068.74)	<0.0001

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*Data expressed as Mean +/- Std Deviation, number (Percentage). P-values for continuous data were obtained using Student's T-test and P-values for categorical data were obtained using Chi-square test.

TABLE 2:

	ALL PATIENTS	**MILD**	**MODERATE**	**SEVERE**	**CRITICAL**	**P VALUE**
CRP(mg/dl)	45.49(9.88-100.86)	20.92(14.8-56.64)	42.71(2.15-87.57)	69.95(15.32-124.58)	95.45(17.98-187.88)	<0.001

*P-values were obtained using Chi-square test.

TABLE3:

CRP AND TERTILES

Variable **CRP**	**Tertile 1 (0-12**(mg/dl)**; n=71)**	**Tertile 2 (12-50**(mg/dl)**; n=62)**	**Tertile 3 (50-300**(mg/dl)**; n=66)**	**P value**
AGE	46.28(29.72-62.84)	55.79(40.4-71.18)	58.27(43.08-73.46)	<0.001
GENDER(M/F)	38/26	43/19	47/19	
CO-MORBIDITIES	23(32%)	42(67%)	49(74%)	<0.0001
HYPERTENSION	13(18%)	24(39%)	31(47%)	0.0013
DIABETES MELLITUS	11(15%)	21(34%)	31(47%)	0.0004
DAYS OF HOSPITALISATION	7.77(4.15-11.39)	11.37(4.47-18.27)	12.04(3.42-20.66)	<0.001
MEAN SPO2 ON ADMISSION	96.88(91.54-102.2) (*2)	91.15(77.6-104.7) (*16)	85.08(69.94-100.22) (*18)	<0.001
REQUIREMENT OF SUPPLEMENTAL O2	4(6%)	46(74%)	56(85%)	<0.0001
REQUIREMENT OF MECHANICAL VENTILATION	1(1%)	23(37%)	35(53%)	<0.0001
ICU ADMISSION	3(4%)	27(44%)	35(53%)	<0.0001
OUTCOME:				<0.0001
Death	2(3%)	20(32%)	35(53%)	
Discharge	69(97%)	42(68%)	31(47%)	

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***** No of patients in each Tertile on oxygen at the time of admission only(excluded from calculation of P values). P-values for continuous data were obtained using ANOVA and for categorical data P-values were obtained using Chi-square test.

Table 4 Relation of CRP with incidence of Severe Covid 19 Positive Cases(N=199)

CRP	Severe Cases(% of total)	Crude (Odds ratio)	Model 1 (Odds ratio)	Model 2 (Odds ratio)
Tertile 1	4(6%)	1(Reference)	1(Reference)	1(Reference)
Tertile 2	25(40%)	9.48E	3.64E	3.64E
Tertile 3	41(62%)	9.79E	7.23E	23.6E

Data are presented as N(%) or odds ratio. Model 1 is adjusted for age, co-morbidities,Hypertension, diabetes mellitus. Model 2 was adjusted for D-dimer, LDH,Ferritin, NLR.

Table 5 Relation of CRP with incidence of in-hospital Mortality in Covid Positive Patients(N=199)

CRP	Death	Crude (Odds ratio)	Model 3 (odds ratio)	Model 4(Odds ratio)
Tertile 1	2(3%)	1	1	1
Tertile 2	20(32%)	8.32E	2.98E	36.3E
Tertile 3	35(53%)	13.7E	21.2E	298E

Data are presented as N(%) or odds ratio. Model 3 is adjusted for age, co-morbidities,Hypertension, diabetes mellitus. Model 4 was adjusted for D-dimer, LDH,Ferritin, NLR

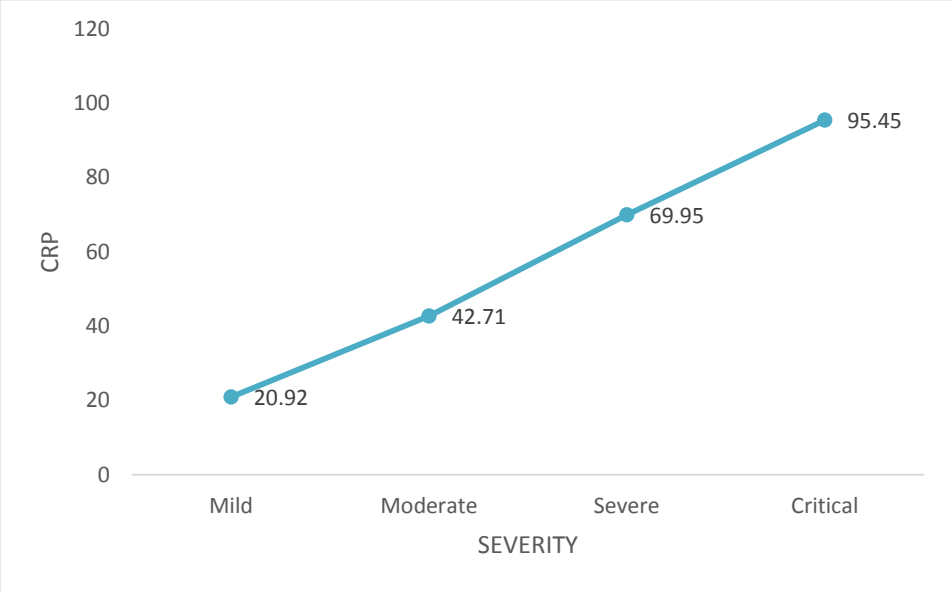

Figure 1: relation between On admission CRP values and different grades of severity. High levels of on admission CRP are associated with increased severity.

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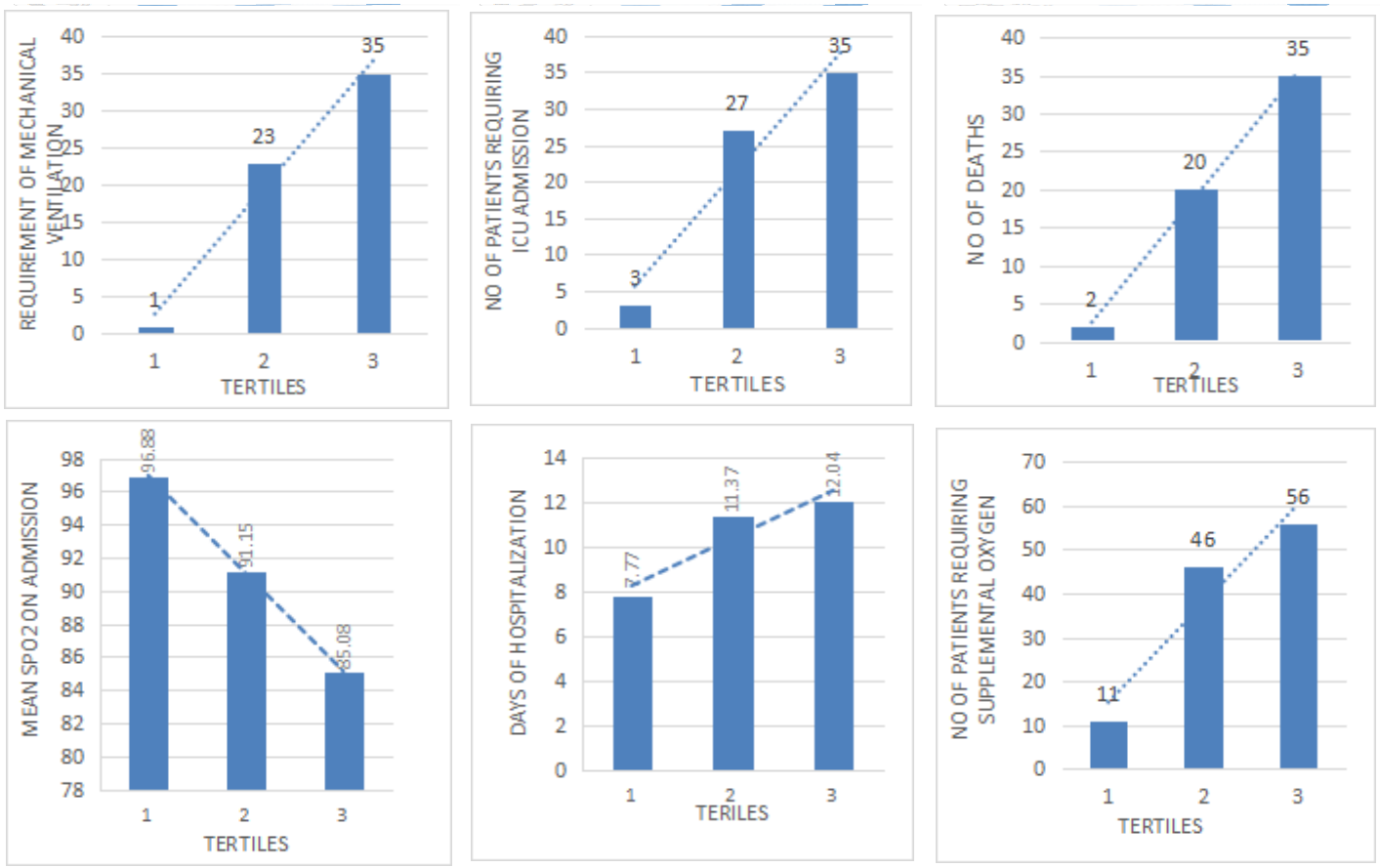

Figure 2: Association between On admission CRP values with Various parameters Indicating Severity

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