Evaluating The Utility of Interleukin-6, C -Reactive Protein (CRP) and Procalcitonin in Predicting Disease Severity and Prognosis in Hospitalized SARS-CoV-2 Patients: A North Indian Retrospective Study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) associated inflammatory cytokine storm that worsens COVID-19, relies heavily on the inflammatory response. IL-6, a TH1 cytokine, PCT and CRP have been linked to serious illness and a higher mortality rate. We further tried to evaluate the role of these indicators and their association with clinical severity in COVID-19 patients.

Material and Methods: Eighty-three consecutive patients with age ≥ 18 years with RT-PCR test positive for SARS-CoV-2 were included in the study. Demographic characteristics (age and sex), underlying co-morbidities, symptoms, physical findings, and laboratory tests of the patients were recorded. All patients were categorized as having mild, moderate, and severe COVID-19 disease, according to the Indian Council of Medical Research (ICMR). The levels of IL-6 and PCT were estimated by electrochemiluminescence immunoassay (ECLIA) using Cobas-e411 Immunoassay System, and Quantitative CRP was done by Unicorn-230 automated biochemistry analyzer to find out their correlation with disease severity and outcome. Multiple Regression was performed to find out factors associated with the adverse outcome of the disease.

Result: Mean age of patients was 51 years. IL-6, CRP, and PCT levels increased in 73 %, 68.0 %, and 8.2 % patients on admission, respectively. The most common co-morbidity associated with the disease was hypertension (25%), followed by diabetes (24%) and respiratory disease (15%). Increased IL-6, CRP, and PCT levels were found in 77 percent, 79 percent, and 20 percent of patients, respectively. We found that IL-6 (P ≤ 0.05), CRP (P ≤ 0.05), and PCT (P ≤ 0.05) were significantly raised in COVID-19 patients with increasing severity of the disease. The Area under the receiver operating characteristic (AUROC) of these parameters ranged between 0.65 and 0.8 (IL-6, 0.828; CRP, 0.809; and PCT, 0.658), indicating a reliable biomarker to assess clinical severity.

Conclusion: Sequential measurement of blood levels of IL-6, CRP, and PCT levels is useful in determining the severity and predicting the outcome of the patients with severe disease. IL-6 and CRP have an independent prognostic

value. On the other hand, the importance of normal PCT concentrations in patients with viral pneumonia needs to be studied further.

Introduction

The concept of COVID-19 related cytokine storm syndrome (COVID-CSS) emerged early in the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) pandemic to explain why some patients exposed to this virus became critically ill with acute respiratory distress syndrome, multi-organ failure, and death. Severe COVID-19 infections have been observed to develop a severe systemic inflammatory response. It is characterized by rapidly changing clinical symptoms and severity, leading to hypoxia, multi-organ failure, and death. However, no reliable indications are yet available to predict illness severity and progression. Various studies have suggested that in addition to direct damage caused by COVID-19, uncontrolled inflammation and release of inflammatory mediators leads to this disease (Z. Liu et al., 2020; F. Liu et al., 2020a; Vatansever & Becer, 2020). Interleukin-6 (IL-6), a pro-inflammatory cytokine, is thought to be involved in developing severe disease. Furthermore, high serum levels of C-reactive protein (CRP), a measure of systemic inflammation, have long been linked to severe disease in bacterial and viral infections (Sproston & Ashworth, 2018), and the same can be predicted for SARS-CoV-2 also. Another critical marker Procalcitonin (PCT), has been found in certain studies to be helpful as a follow-up marker for predicting outcomes in septic or critically unwell patients (Clec'h et al., 2004). The objective of the current study is to evaluate the dynamics and utility of IL-6, PCT, and CRP in predicting severity of disease and prognosis in COVID-19 patients.

Material and Methods

Study participants

Eighty-three consecutive patients with age ≥ 18 years with an RT-PCR test positive for SARS-CoV-2 between 1 March 2020 and 8 April 2020, who were admitted to COVID-Wards/ICU in JNMCH, a tertiary care center in the Aligarh region of North India, were included in this retrospective study. All the patients were confirmed COVID-19 positive as detected by RT-PCR (Chang et al., 2020 Sami et al., 2021). All patients were categorized as having mild, moderate, and severe COVID-19 disease as advised by the Indian Council of Medical Research (https://www.icmr.gov.in/pdf/covid/techdoc/COVID_Management_Algorithm_17052021.pdf). Briefly, Mild covid-19 disease was defined as upper respiratory tract symptoms (with or without fever) without shortness of breath or hypoxia; moderate COVID-19 disease was defined as respiratory rate > 24/min, breathlessness, or SpO2: 90 percent to 93 percent on room air; and severe COVID-19 disease was defined as respiratory rate >30/min, breathlessness, or SpO2: 90 percent to 93 percent on room air.

Demographic characteristics (age and sex), underlying co-morbidities, symptoms, physical findings, and laboratory tests were collected from the patients with the help of a predefined questionnaire. All the patients were tested for IL-6, CRP, and PCT levels.

Determination of IL-6

The IL-6 concentration was measured using the Roche Diagnostic Cobas-e411

Immunoassay System, which is a fully automated, random access, software-controlled immunoassay analysis system based on the ECLIA method. The results were analyzed as Normal: 0-7 pg/ml; Raised: >7 pg/ml.

Determination of CRP

Automated Biochemistry Analyzer Unicorn-230 was used to measure the concentration of CRP in serum. The results were analysed as Normal: 0-6 mg/l; Raised: >6 mg/l.

Determination of PCT

PCT concentration was measured by Cobas-e411 Electrochemiluminescence Immunoassay Analyzer (ECLIA). The results were analyzed as "No risk of sepsis" :<0.046 ng/ml; "moderate risk of Sepsis": 0.046-0.05ng/ml; "High risk of sepsis": >2 ng/ml.

Statistical Analysis

For statistical analysis, IBM's Statistical Package for the Social Sciences Software (SPSS) version 25.0 (Chicago, IL) was utilised. Means and percentages were used to represent continuous and categorical data, respectively. Wherever possible, the Mann-Whitney U test, 2 test, or Fisher's exact test was employed to compare continuous and categorical variables. The predictive value of serum IL-6, CRP, and PCT was determined using the receiver operating characteristic curve (ROC). Multiple Regression was performed to find out factors associated with adverse outcomes of the disease.

Results

Baseline characteristics of the 83 patients included in the study, stratified by disease severity, are displayed in Table 1. The mean age was 51 ± 16.18, and there was no significant difference in the male to female ratio between the groups. Fever (68 patients, 90%) was the most common symptom followed by cough (57 patients, 67%) and difficulty in breathing (45 patients, 54%) and while a few patients (69 patients, 31.3%) had other symptoms such as fatigue (37 patients, 54%) and sore throat (16 patients, 19%). The majority of the patients in our study had one or more underlying comorbid conditions. Hypertension (21 patients, 25 %), diabetes mellitus (20 patients, 24 %), and pre-existing respiratory disease were the most prevalent co-morbidities (13 patients, 15 %). As per the ICMR Guidelines,14 patients (8.1%) belonged to mild disease, 45 patients (27.6%) belonged to moderate disease, and 24 patients (39.4%) belonged to the severe disease category, respectively.

Table 1. Demographic characteristics and Clinical symptoms of 83 patients with Covid-19

		Total n=83	Mild Covid-19 (n=14)	Moderate Covid-19 (n=45)	Severe Covid-19 (n=24)	p-value
Age (Mean ±SD)	Total	51.94(±16.18)	52.19(±15.81)	48.82(±14.54)	54.71(±17.19)	0.76
	Males	51.9(±17.7)	49.67(±19.4)	(17.2) 47.85	60.50(±16.2)	0.34
	Females	50.08(±13.9)	54.25(±13.5)	50.16(±13.3)	46.60(±15.8)	0.76
Sex	Males	46 (55%)	6 (13%)	26 (57%)	14 (30%)	0.58
	Females	37 (44%)	8 (22%)	19 (51%)	10 (27%)	
Comorbidities	Hypertension	21 (25%)	1 (5%)	12 (57%)	8 (38%)	0.02
	Diabetes	20 (24%)	1 (5%)	8 (40%)	11 (55%)	0.35
	Respiratory disease	13 (15%)	1 (8%)	7 (54%)	5 (38%)	0.74

Vaccination Status	Vaccinated	12 (14%)	2 (17%)	6 (50%)	4 (33%)	0.63
	Not Vaccinated	71 (86%)	12 (17%)	39 (55%)	20 (28%)	0.42
Clinical symptoms	Fever	68 (90%)	11 (16%)	36 (53%)	21 (31%)	0.91
	Cough	57 (67%)	10 (17%)	29 (51%)	18 (32%)	0.85
	Fatigue	37 (44%)	5 (13%)	19 (51%)	13 (35%)	0.81
	Difficulty in breathing	54%))45	0	25 (55%)	20 (44%)	NA
	Sore Throat	16 (19%)	3 (19%)	8 (50%)	5 (31%)	0.68

Table 2 and Figure 1 summarize IL-6, CRP, and PCT levels in COVID-19 patients. IL-6, CRP, and PCT levels were raised in 77%, 79%, and 20% of patients on admission, respectively. We found that IL-6 ($P \leq 0.05$), CRP ($P \leq 0.05$), and PCT ($P \leq 0.05$) were significantly raised in COVID-19 patients when compared with the increased severity of the disease. Higher PCT levels (>2 ng/ml) were seen in patients suffering from severe COVID-19 disease.

Table 2. Serum levels of IL-6, CRP, and PCT in patients with Covid-19

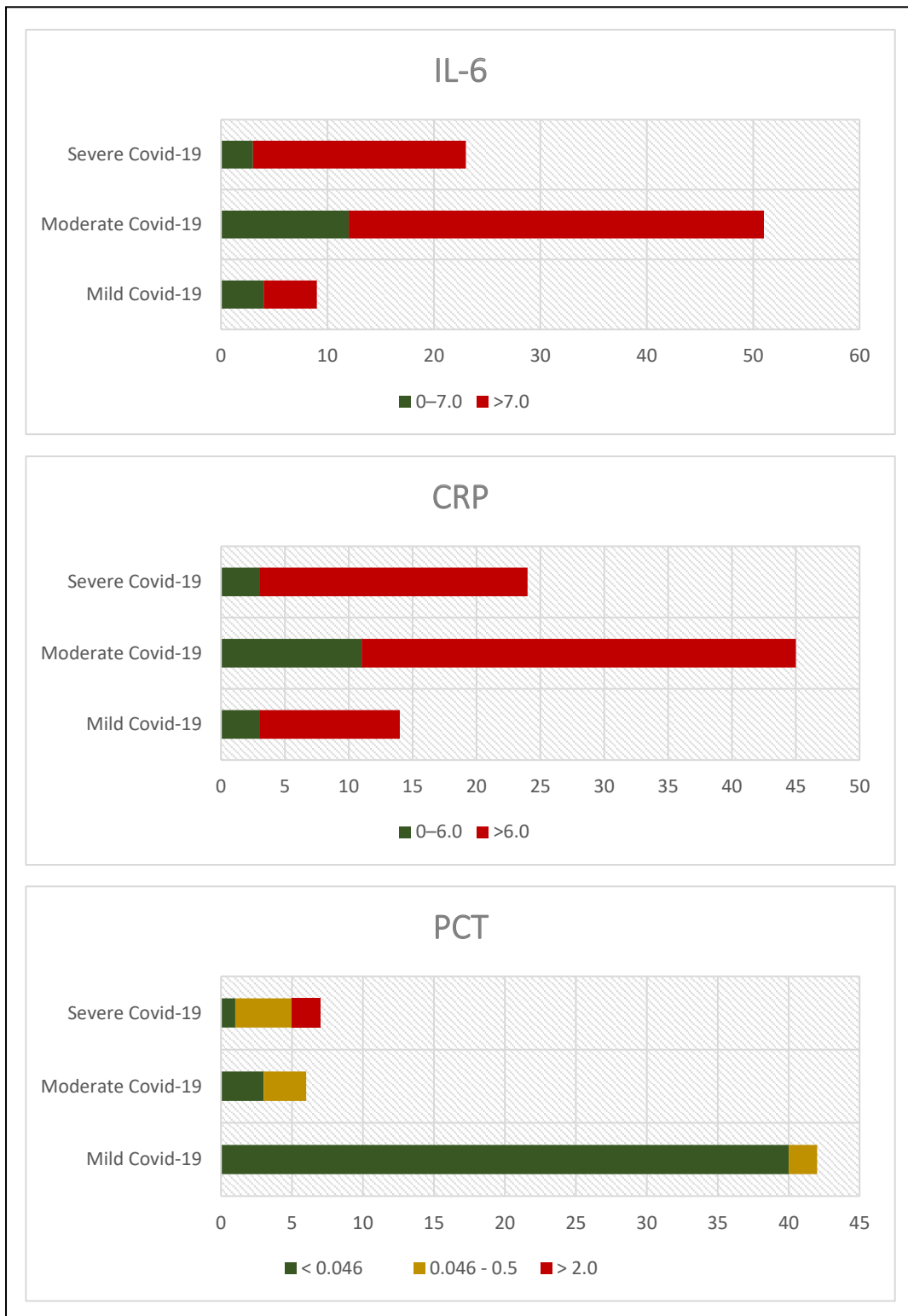| Biomarker (Unit)	Concentration	Total	Mild Covid-19	Moderate Covid-19	Severe Covid-19	p-value
CRP (mg/L) (n=83)	6.0 (Normal)–0	17 (20%)	3	11	3	.016
	>6.0 (Elevated)	66 (79%)	11	34	21	
IL-6 (pg/mL) (n=83)	7.0 (Normal)–0	19 (11%)	4	12	3	.018
	>7.0 (Elevated)	64 (77%)	5	39	20	
PCT (ng/mL) (n=55)	< 0.046 (No risk of Sepsis)	44 (80%)	40	3	1	.009
	0.046 - 0.5 (Moderate risk of sepsis)	9 (16%)	2	3	4	
	> 2.0 (Severe risk of Sepsis)	2 (4%)	0	0	2	

Figure 1. Association of IL-6, CRP and PCT with Disease severity

Figure 2 and Table 3 show the ROC curve for IL-6, PCT, and CRP levels associated with poor prognosis. The Area under curve (AUC) for IL-6 and CRP is >0.75, providing strong evidence about its predictive function and is statistically significant. Though PCT with AUC 0.658 can be a predictor but not statistically significant.
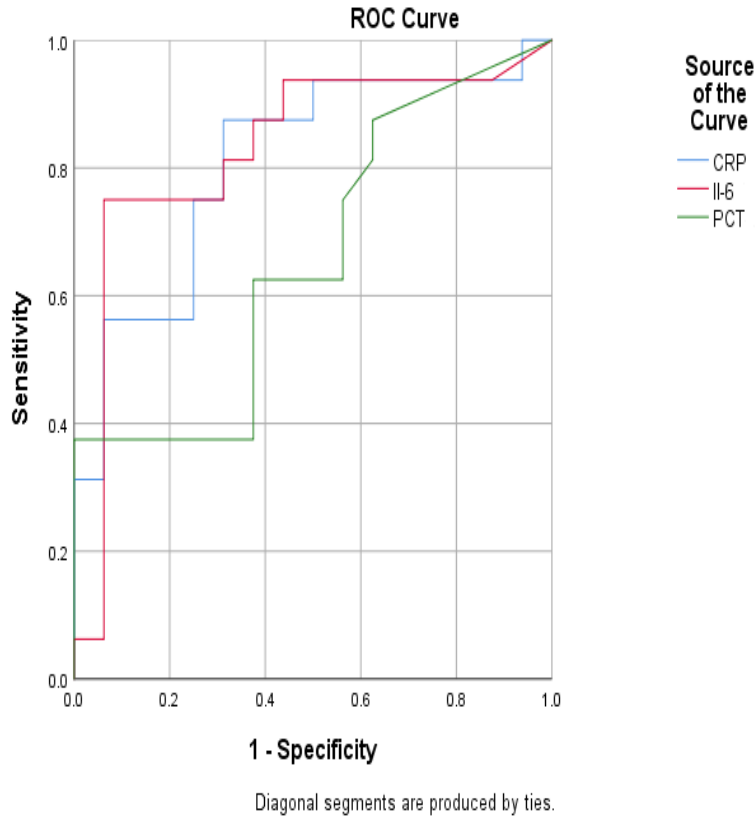
Figure 2. Receiver operating characteristic curve of C-reactive protein (CRP), interleukin-6 (IL-6) and Procalcitonin (PCT) in patients with COVID-19 with poor prognosis.

Table 3. Biomarkers (CRP, IL-6 and PCT) and Area under the curve

Test Result Variables	Area	Std. Error	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	.809	.079	.003	.654	.963
IL-6	.828	.080	.002	.670	.986
PCT	.658	.098	.127	.466	.851

IL-6 and CRP are the markers of systemic inflammation that herald the onset of COVID-19 disease and its complications. To explore the possibility of using only CRP levels in resource limited and financially constrained settings, we performed Linear Regression to analyse the correlation between the levels of CRP as a predictor of IL-6 level. We found out that the levels of CRP had simple correlation coefficient of only 0.292 signifying that only in 29.2% of COVID-19 patients, the levels of CRP and IL-6 show hardly any level of correlation; even more, the total variation in the levels of IL-6 as predicted by CRP levels was only 8.5% (R^2=.085); The mean of the error between the actual and predicted levels of IL-6 based on CRP levels was 473%, which is very large.

Multiple Regression was also run to predict the bad outcome (death and complications) from the levels of Biomarkers (IL-6, PCT, and CRP) and the presence of Co-morbidities (diabetes and hypertension). The regression model was a good fit for the data. These variables statistically significantly predicted bad outcome, $F_{(5, 26)} = 6.8$, $p < .001$, $R^2 = .536$. Levels of CRP, IL-6, and hypertension variables added statistically significantly

to the prediction, p < .05, while the levels of PCT and diabetes did not add statistically significantly to the prediction.

Discussion

The ability to interpret Coronavirus disease-2019 (COVID-19) dynamics requires accurate assessments of the risk of developing symptoms and progressing to critical illness in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Moreover, biomarkers and cytokines appear to be helpful, cost-effective tools for guiding treatment in COVID-19 infection.

The mean age of hospitalized COVID-19 positive patients in our study was 51.94 years, and it did not differ significantly among the three categories (Mild, Moderate, Severe). Increased age has been reported as a risk factor for hospitalization and increased duration of hospital stay by various studies (Pijls et al., 2021). Patients over 60-year-old had multiple clinical symptoms, a more severe illness, and a longer course than those under 60-year-old. (Y. Liu et al., 2020). Old-age people with COVID-19 are more likely to develop co-morbidities and have a lower reserve capacity of critical organs, leading to greater fragility. This, combined with an aging immune system, can lead to a poor outcome and a higher chance of mortality in these patients.

Various studies have also found the association of the male gender with severe disease (Pijls et al., 2021) (Karlberg et al., 2004); we, however, have not found any such difference. In this study, the disease was equally distributed among both sexes. Also, according to epidemiological reports based on infectious disease notification, the prevalence of COVID-19 is similar in both sexes. (Raimondi et al., 2021) (http://globalhealth5050.org/covid19.) http://globalhealth5050.org/covid19. (https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_13maggio%20ITA.pdf.)

Previous research has shown that co-morbidities like Diabetes, COPD, hypertension and cancer might contribute to a worse prognosis (Cheng et al., 2021) (Hassan, 2020) (Honardoost et al., 2021). We discovered that the existence of hypertension, diabetes, and respiratory disease was strongly linked to the severity of the disease. However, only hypertension was significantly associated with predicting bad outcomes. Surprisingly, Diabetes did not have a statistically significant association with the adverse outcome at our center, contrary to what was reported in other studies (N. Zhang et al., 2020); this may be due to better glycemic controls and increased care, and early therapeutic intervention in these patients.

Only 14 % of our patients were vaccinated, again pointing to the importance of vaccination as the lower vaccination rate in these patients led to their hospitalization. In its weekly report, the CDC also emphasized vaccination's importance in reducing hospitalization (Rosenberg, 2021). Vaccine may serve as a break in chain of disease and hence decrease disease transmission (Shahid, et al., 2021)

The uncontrolled inflammatory response in COVID-19 infection is associated with severe disease (Del Valle et al., 2020). Supporting the theory, high levels of inflammatory markers such as CRP, PCT, and elevated levels of inflammatory cytokines and chemokines have been found in patients with severe illnesses. (Marimuthu et al., 2021) (F. Liu et al., 2020b). In our study, IL-6, CRP, and PCT levels increased considerably in 77%, 79%, and 20% of patients, respectively, confirming the idea of "cytokine storm"(F. Liu et al., 2020c) and indicated that inflammatory variables played a vital role in the disease, and

the levels of IL-6, CRP, and PCT was much higher than in patients with severe disease as compared with the milder form. The rise in levels of all three markers corresponding to disease severity was statistically significant, indicating that IL-6, CRP, and PCT might be used as independent factors to predict the development of severe disease in COVID-19.

IL-6 is a multifunctional cytokine that regulates immune cells and communicates between cells. This factor is implicated in inflammation, tumors, and hematological disorders, and it has a considerable pro-inflammatory effect, and a range of biological activities (Tanaka et al., 2014) IL-6 has been identified as the primary source of cytokine storms in Covid-19 patients. (Santa Cruz et al., 2021). Various studies have shown peripheral blood IL-6 levels might be used as an independent predictor of COVID-19 progression (Del Valle et al., 2020) (F. Liu et al., 2020a) (Gorham et al., 2020), which is consistent with the findings of this study.

CRP is a sensitive biomarker of inflammation, infection, and tissue damage generated in the liver in response to IL-6 (Sproston & Ashworth, 2018). This study examined the association between CRP levels in COVID-19 patients and conclude that CRP level is a better predictor of moderate and severe disease development with a significant P-value.

PCT is a non-hormonal glycoprotein that is the precursor to calcitonin (F. Liu et al., 2020b). PCT levels in the blood are frequently low or undetectable. (Samsudin & Vasikaran, 2017) Several studies have recently found that increased PCT levels are linked to the severity of COVID-19 (J.-J. Zhang et al., 2020) (Hu et al., 2020). We also found that on comparison of levels with disease severity in Covid-19, the difference was statistically significant.

When we explored the possibility of using only CRP levels in resource limited and financially constrained settings as a predictor of IL-6 level (Sproston & Ashworth, 2018), we found no correlation between them, as also reported by several other studies (Lavillegrand et al., 2021), although physiologically related, changes in circulating levels of CRP and IL-6 may not always track with one another regarding the severity of COVID-19 disease, its prognosis and outcome. Hence, we do not recommend to rely only on the CRP only to assess the clinical condition of COVID-19 Patients.

There are certain limitations to this study. First, the number of cases was limited due to the study's single-centre design. Secondly, clinical data were scarce as we do not have a digital patient record system.

Conclusion

Serum levels of IL-6 and CRP have a substantial relationship with COVID-19 severity and can be utilized as independent predictors of a bad outcome. The validity of PCT, on the other hand, has to be studied further. The presence of hypertension in COVID-19 patients is associated with a bad outcome. Increased vaccination coverage can reduce hospitalization in COVID-19 Patients.

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تقييم فائدة Interleukin-6 وC-Reactive Protein (CRP) وProcalcitonin في توقع شدة المرض والتشخيص في مرضى SARS-CoV-2 في المستشفى: دراسة استعادية شمال الهند

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المُستَخلَص

الخلفية: يعتمد مرض فيروس كورونا 2019 (COVID-19) المرتبط بعاصفة السيتوكينات الالتهابية التي تفاقم COVID-19 بشكل كبير على الاستجابة الالتهابية. تم ربط IL-6 و TH1 cytokine وPCT وCRP بمرض خطير وارتفاع معدل الوفيات. حاولنا كذلك تقييم دور هذه المؤشرات وارتباطها بالخطورة السريرية في مرضى COVID-19.

المواد والطرق: تم تضمين ثلاثة وثمانين مريضًا متتاليًا بعمر 18 عامًا مع اختبار RT-PCR إيجابيًا لـ SARS-CoV-2 في الدراسة. تم تسجيل الخصائص الديموغرافية (العمر والجنس) والأمراض المشتركة الكامنة والأعراض والنتائج الجسدية والاختبارات المعملية للمرضى. تم تصنيف جميع المرضى على أنهم مصابون بمرض COVID-19 الخفيف والمتوسط والشديد ، وفقًا للمجلس الهندي للبحوث الطبية (ICMR). تم تقدير مستويات IL-6 وPCT بواسطة المقايسة المناعية للتلألؤ الكهربائي (ECLIA) باستخدام نظام المقايسة المناعية Cobas-e411، وتم إجراء CRP الكمي بواسطة محلل الكيمياء الحيوية الآلي Unicorn-230 لمعرفة ارتباطها بخطورة المرض ونتائجه. تم إجراء الانحدار المتعدد لمعرفة العوامل المرتبطة بالنتائج السلبية للمرض.

النتيجة: كان متوسط عمر المرضى 51 سنة. زادت مستويات IL-6 وCRP وPCT في 73 ٪ و68.0 ٪ و8.2 ٪ من المرضى عند القبول، على التوالي. وكانت أكثر حالات الاعتلال المشترك المرتبطة بالمرض هي ارتفاع ضغط الدم (25٪)، يليه مرض السكري (24٪) وأمراض الجهاز التنفسي (15٪). تم العثور على زيادة مستويات IL-6 وCRP وPCT في 77 بالمائة و79 بالمائة و20 بالمائة من المرضى على التوالي. وجدنا أن IL-6 (P≤0.05) وCRP (P≤0.05) وPCT (P≤0.05) قد تم رفعها بشكل كبير في مرضى COVID-19 مع زيادة شدة المرض. تراوحت المنطقة الواقعة تحت خاصية تشغيل المستقبل (AUROC) لهذه المعلمات بين 0.65 و0.8 (0.828 ،IL-6؛ 0.809 ، CRP؛ و0.658 ، PCT)، مما يشير إلى علامة بيولوجية موثوقة لتقييم الشدة السريرية.

الخلاصة: القياس المتسلسل لمستويات الدم لـ IL-6 وCRP وPCT مفيد في تحديد شدة الحالة والتنبؤ بنتائج المرضى المصابين بمرض حاد. IL-6 وCRP لهما قيمة تنبؤية مستقلة. من ناحية أخرى ، فإن أهمية التركيزات الطبيعية لمعاهدة التعاون بشأن البراءات في مرضى الالتهاب الرئوي الفيروسي تحتاج إلى مزيد من الدراسة.

مفاتيح الكلمات: إنترلوكين 6، سي آر بي، بروكالسيتونين، كوفيد - 19.