C-reactive protein as a prognostic indicator in COVID-19 patients

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Abstract

While some biomolecules have been explored to identify potential biomarkers for prognosis of the COVID-19 prognosis, there are no reliable prognostic indicators of disease progression and severity. We aimed to evaluate the ability of the C-reactive protein (CRP) to predict COVID-19 infection.

This retrospective study was conducted on 429 patients diagnosed with COVID-19 between March 30, 2020, and April 30, 2020. The study population was divided into severe cases (n = 175) and nonsevere cases (n = 254). Data on demographic characteristics, clinical features, and laboratory findings on admission were collected.

The proportion of patients with increased CRP levels was significantly higher in severe cases than in nonsevere patients. Analysis of ROC curve found that CRP could be used as an independent factor in predicting the severity of COVID-19 infection. Also, patients with CRP > 64.75 mg/L were more likely to have severe complications.

The serum levels of CRP can predict the severity and progression of illness in patients with COVID-19.

Introduction

Since December 2019, a new type of coronavirus called coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified in China (1). The COVID-19 pandemic, then spread quickly around the world [2,3]. By August 16, 2020 there have been 21 294 845confirmed cases of COVID-19, including 761 779 deaths, reported to the World Health Organization (WHO) [4]. The rapid spread of the SARS-CoV-2, rapid changes in clinical features and increased mortality have become the biggest problem in the world. Furthermore, there are no reliable prognostic indicators of disease progression. Recently, some studies have reported that C-reactive protein (CRP) levels can be used in the early diagnosis of pneumonia and that higher levels of CRP were associated with severe pneumonia [5]. Current research aims to evaluate CRP levels and disease progression in order to provide a reference for clinical management.

Materials And Methods

2.1.Study design, participants and definition

The present protocol of retrospective study has been approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (Code: IR.MUBABOL.REC.1399.041). The three affiliated hospitals at Babol University of Medical Sciences has been designed to treat patients with COVID-19. A total of adult 429 cases of COVID-19 were confirmed at these centers from March 30, 2020, to April 30, 2020. All patients with COVID-19 who enrolled in the recent study were diagnosed according to the WHO interim guidance for COVID-19 (6th edition) [6]. In other word, all patients with the physician- and laboratory-confirmed (positive in nasopharyngeal/ throat swab specimens by reverse transcription polymerase chain reaction (RT-PCR)) COVID-19 infection were included, while suspected cases with similar clinical symptoms were excluded. All cases were monitored using the clinical data collected until March 30, 2020. One of the following criteria was used to determine severe COVID-19 illness: 1) respiratory rate ≥30 bpm; 2) oxygen saturation ≤93 %; 3) arterial oxygen partial pressure (PaO2)/oxygen concentration (FiO2) ≤300 mmHg; 4) intensive care units (ICU) admission.

2.2.Data collection

Patient medical records were reviewed by an experienced team of clinicians of the Infectious Diseases Research Center of Babol University of Medical Sciences. The epidemiological, clinical, laboratory, radiological findings, and outcomes data

were collected using a data collection checklist from electronic medical records. Moreover, recorded patient data included demographic information, past medical history (PMH), underlying medical conditions, symptoms, and para-clinical data.

2.3.Statistical analysis

The statistical data was analyzed by using SPSS 16.0 (IBM, Chicago, IL, USA). Continuous and categorical variables were presented as median (IQR) and n (%), respectively. Mann-Whitney U test, χ^2 test, or Fisher's exact test was used to compare continuous and categorical variables.

The predictive value of the CRP was evaluated by measuring the area under the receiver operating characteristic curve (AUROC). The optimal threshold value was obtained by calculating the Youden index. A multivariate Cox proportional risk model was used to determine predictive factors for disease risk.

Results

There were 429 patients with COVID-19 in our study. Of thsese, 175 patients (40.8%) were assigned to a severe group, while 254 patients (59.2%) developed into non-severe cases. Demographic and clinical characteristics are summarized in Table 1. The mean age was 57.21±16.18 years with an age from 16 to 99 years. The average age was higher in the severe group compared with the non-sever group (p=0.111). One hundred and eighty-six (43.4%) were female. The severe ratio for males was higher than for females but this difference was not significant (p=0122). The median duration from illness onset to discharge was 7 days. Overall, dyspnea (72.5%) was the most common initial symptom, followed by fever (61.3%), dry cough (57.6%). However, there was no significant difference in the symptoms ratio between the two groups. Nearly, half of the patients (213, 49.7%) had comorbidities, diabetes (27.7%), cardiovascular disease (24.9%), hypertension (22.8%) were the most common comorbidities. Sixty two patients (14.5%) had a complication, including the occurrence of acute respiratory distress syndrome (ARDS) (18[10.3%] vs 0[0], P= 0.101), acute heart failure (9 [5.1%] vs 19 [7.5%], P= 0.335) and arrhythmia (8 [4.6%] vs 11 [4.3%], P= 0.905) (Table1). Laboratory findings for the patients are presented in Table2. Median levels of Lymphocyte percent, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lactate dehydrogenase (LDH) were not in the normal range. Severe group had a significantly higher ESR (MD: 57.5 vs MD: 40 , P=0.005) , CRP (MD: 97 vs MD: 50, p<0.001), LDH (MD: 783.5 vs MD: 459, p<0.001), and lower lymphocytes percent (MD: 12 vs MD: 22.7, p<0.001) compared to non-severe group.

Analysis of the ROC curve indicated an area under the curve (AUC) for CRP levels as a predictor of severity with 0.706 (95% CI, 0.649-0.764; p<0.001). The AUROC of this marker indicating a high diagnostic value for clinical severity and the optimal threshold value was 64.75 mg/L with a sensitivity of 71.32% and specificity of 60% (Table3 and Figure1). We reclassified patients into two groups according to the optimal CRP threshold (cut-off: 64.75). The proportion of severe patients with a CRP higher than the optimal threshold was significantly different compared to CRP lower than these values (p<0.001).

The univariate analysis used to logistic model indicated the severity was associated with hospital admission (OR, 1.166; 95% CI, 1.119-1.216; P<0.001), BUN (OR, 1.027; 95% CI, 1.014-1.040; P<0.001), lymphocyte (OR, 0.917; 95% CI, 0.895-0.939; P<0.001), and CRP (OR, 3.647 95% CI, 2.288-5.813; P<0.001). As determined by multivariate analysis, hospital admission (OR, 1.185; 95% CI, 1.086-1.293; P<0.001) and CRP (OR, 3.826; 95% CI, 1.166-12.560; P=0.027) were significantly associated with severity, the patients with CRP>64.75 were more likely to severity (Table4).

Discussion

In the present retrospective study, the clinical characteristics of severe COVID-19 patients have compared their clinical features with those of nonsevere patients and also analyzed the possible factors associated with disease progression and severity. Furthermore, the prognostic value of the CRP in the progression of COVID-19 cases has been revealed. The current study presented the association between CRP and COVID-19 infection and also found that cases with CRP > 64.75 mg/L

were more likely to develop severe disease. In other words, ROC analysis confirmed CRP as a valuable predictor of disease progression in COVID-19 infection.

In response to infections, the liver synthesizes great quantities of acute-phase proteins (APPs) such as CRP [7,8]. This acute inflammatory protein is a highly sensitive biomarker for inflammation, tissue damage, and infection [9]. It has been shown that CRP levels are correlated with levels of inflammation [10]. CRP levels can promote phagocytosis and activate the complement [11]. In other words, CRP binds to microorganisms and promotes their removal through phagocytic cells [12].

The serum CRP level is routinely low but increases during inflammatory responses. As shown, this biomarker may be raised by viral or bacterial infections. It is important to note, CRP levels have significantly increased in bacterial infections compared to viral infections [13]. The current study revealed that significantly higher CRP levels in severe cases than nonsevere patients, which suggested that CRP may be a biomarker of disease severity and progression in COVID-19 infection. Liu et al. reported that significantly more severe cases infected with COVID-19 experienced higher CRP levels versus non-severe patients [14]. Qin et al. presented that higher levels of CRP in severe COVID-19 patients compared to non-severe cases suggest that this serum marker may be monitored for evaluate disease progression [15]. As shown, all of these cases are similar to the results of the present study; CRP can be a predictive factor for disease progression in COVID-19. The limitations of the research were the small sample size and some limitations of the clinical data.

Conclusion

Serum CRP levels could be used as an important indicator of the severity of COVID-19 and also, the present study suggests that patients with high levels of CRP should be sufficiently monitored.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic data and baseline characteristics of patients infected with COVID-19

		All patients (n=429)	Severe (n=175)	Non severe (n=254)		p-value
Age, mean±SD (rang)		57.21±16.18 (16-99)	58.75±15.88 (22-97)	56.18±16.32 (16-99)	1.59	0.111
Sex	male	241(56.4)	106(60.9)	135(53.4)	2.39	0.122
	female	186(43.6)	68(39.1)	118(46.6)		
Hospital admission(days)		7(1-37)	10(1-37)	6(1-31)		<0.001
Clinical symptoms						
	Fever	263(61.3)	105(60)	158(62.2)	0.21	0.645
	Fatigue	161(37.5)	70(40)	91(35.8)	0.77	0.380
	Headache	76(17.7)	31(17.7)	45(17.7)	0.00	1.000
	Dry-Cough	247(57.6)	98(56)	149(58.7)	0.003	0.584
	Sore Throat	36(8.4)	19(10.9)	17(6.7)	2.33	0.126
	Expectorationn	83(19.3)	34(19.4)	49(19.3)	0.001	0.972
	Hemoptysis	7(1.6)	3(1.7)	4(1.6)	0.013	0.911
	Chest Pain	61(14.2)	22(12.6)	39(15.4)	0.658	0.417
	Dyspnea	311(72.5)	126(72)	69(72.8)	0.036	0.849
	Nausea	81(18.9)	37(21.1)	44(17.3)	0.987	0.320
	Diarrhea	25(5.8)	12(6.9)	13(5.1)	0.517	0.450
	Constipation	24(5.6)	9(5.1)	15(5.9)	0.114	0.736
	Anorexia	118(27.5)	53(30.3)	65(25.6)	1.14	0.284
	Arthralgia	48(11.2)	20(11.4)	28(11)	0.017	0.896
	Stomachache	39(9.1)	16(9.1)	23(9.1)	0.001	0.975
	Dizziness	54(12.6)	21(12)	33(13)	0.093	0.761
	Loss ofsmell and taste	18(4.2)	9(5.1)	9(3.5)	0.659	0.417
Comorbidity						
	Hypertension	98(22.8)	32(18.3)	66(26)	3.48	0.062

	Cardiovascular disease	107(24.9)	38(21.7)	185(27.2)	1.64	0.200
	Diabetes	119(27.7)	49(28)	70(27.6)	0.010	0.920
	Cancer	10(2.3)	3(1.7)	7(2.8)	0.494	0.482
	Chronic liver disease	5(1.2)	3(1.7)	2(0.8)	0.773	0.379
	Chronic kidney disease	17(4)	2(1.1)	15(5.9)	6.17	0.013
	Brain disease	9(2.1)	6(3.4)	3(1.2)	2.54	0.110
	COPD	14(3.3)	7(4)	7(2.8)	0.508	0.476
Complication						
	Nosocomial pneumonia	8(1.9)	2(1.1)	6(2.4)	0.842	0.359
	Urinary tract infections	6(1.4)	2(1.1)	4(1.6)	0.140	0.708
	Shock	5(1.2)	5(2.8)	0(0)	3.22	0.073
	Acute heart failure	28(6.5)	9(5.1)	19(7.5)	0.928	0.335
	Arrhythmia	19(4.4)	8(4.6)	11(4.3)	0.014	0.905
	ARDS	18(4.2)	18(10.3)	0(0)	2.68	0.101
	Acute kidney failure	1(0.4)	0(0)	1(0.4)	0.691	0.406

Note: P values of the variables comparing severe and nonsevere patients are from t-test. Data are n (%) unless otherwise stated. **Abbreviation:** ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease

Table 2 Laboratory findings of severe and non- severe COVID-19 cases

	Normal range	Severe (n=175)	Non severe (n=254)	P-value
White blood cell count, median (range), cmm	4500-11000	9100 (1700-42300)	6500 (2100-157000)	<0.001
Lymphocytes %, median (range)	26-46	12 (2-36)	22.7 (3-75)	<0.001
Hemoglobin, median (range), (g/dL)	13.5-18	11.95 (6-21)	12.5 (5.3-22.3)	0.032
Erythrocyte sedimentation rate, median (range), mm/h	0-15	57.5 (3-128)	40 (2-140)	0.005
C-reactive protein, median (range), mg/L	0-10	97 (1-440)	50 (4-392)	<0.001
Platelet count, median (range), mL	140000-450000	197000 (42000-568000)	197000 (8000-1081000)	0.839
Blood urea nitrogen, median (range), mg/dl	10-20	19 (5-158.2)	15 (4-150)	<0.001
Creatinine, median (range), mg/dL	0.7-1.4	1 (0.5-7.4)	1 (0.5-7.3)	0.360
Lactate dehydrogenase, median (range), U/L	140-280	783.5 (146-2436)	459 (30-2500)	<0.001
Sodium, median (range), mmol/L	135-145	135 (117-146)	136 (120-152)	0.144
Potassium, median (range), mmol/L	3.7-5.2	4.1 (3-8.2)	4.1 (2.9-5.5)	0.961

Note: P values of the variables comparing severe and nonsevere are from t-test. Data are n (%) unless otherwise stated.

Area under the ROC curve and optimal cut-off value of CRP**Table 3**

AUC	Optimal cut-off value	sensitivity	specificity	Predictive value		Likelihood ratio	
				Negative	Positive	Positive	Negative
0.706	64.75mg/L	71.32%	60%	78.11%	50.55%	0.48	1.76

Table 4 Univariate and multivariate analyses used to logistic regression model

Variable	Univariate		Multivariate	
	Odds Ratio(95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age	1.010 (0.998-1.022)	0.112	1.003 (0.963-1.030)	0.762
Hospital admission(days)	1.166 (1.119-1.216)	<0.001	1.185 (1.086-1.293)	<0.001
lymphocyte	0.917 (0.895-0.939)	<0.001	0.990 (0.934-1.050)	0.741
BUN	1.027 (1.014-1.040)	<0.001	1.045 (0.994-1.097)	0.082
Diabetes	1.022 (0.665-1.571)	0.920	2.543 (0.809-7.998)	0.110
CRP	3.647 (2.288-5.813)	<0.001	3.826 (1.166-12.560)	0.027

Abbreviation: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; CRP, C-reactive protein; CI, confidence interval. *Statistically significant.