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Research Paper

Baseline CRP Levels and Thromboembolic Events: A Retrospective Case-Control Study

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ABSTRACT

Background: Several studies have proposed that C-reactive protein (CRP) levels could serve as a potential indicator for predicting coronavirus disease 2019 (COVID-19); however, the findings have been inconsistent. This study aims to evaluate the relationship between baseline CRP and thromboembolic complications in patients with COVID-19.

Methods: This case-control study involved two groups of COVID-19 patients admitted to Shahid Beheshti Hospital in Kashan: those with thromboembolic events (TEEs) and those without. Eligible patients were enrolled through simple random sampling based on predefined inclusion criteria. Data on patient demographics, clinical findings, and vital signs were collected using a standardized checklist.

Results: We examined 70 patients with COVID-19 who experienced TEEs and 70 patients who did not. The most common underlying conditions in both groups were high blood pressure, affecting 21 individuals (30%), and diabetes, affecting 25 individuals (35.7%) ($P > 0.05$). In the control group, the most prevalent clinical symptoms associated with TEEs were shortness of breath, reported by 60 individuals (85.7%), and cough, reported by 46 individuals (65.7%). The incidence of shortness of breath in the case group was significantly higher than in the control group ($P < 0.001$). Additionally, the two groups showed significant differences in breathing rate ($P = 0.002$) and heart rate ($P = 0.016$). There was also a significant difference in CRP levels between the two groups ($P = 0.038$), with patients in the case group exhibiting higher CRP levels.

Conclusion: This finding indicated that the level of CRP in patients with TEEs was significantly higher than in the control group. These results suggest that CRP may serve as an effective marker for identifying patients at risk of TEEs.

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Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic with unprecedented challenges [1]. The primary pathogenesis of COVID-19 involves severe pneumonia, often accompanied by renal damage, neurological involvement, and acute myocardial infarction [2]. Patients with COVID-19 frequently exhibit an unexplained increase in blood levels of cytokines and chemokines, which can lead to a cytokine storm [3]. Studies indicate that, during the inflammatory response and cytokine storm, levels of CRP and other inflammatory factors rise, with elevated levels correlating to a more severe response in patients [4]. Research has consistently shown that CRP levels are elevated in patients with COVID-19 [5].

In contrast to the erythrocyte sedimentation rate, which serves as an indirect measure of inflammation, CRP levels increase and decrease rapidly in response to the onset and resolution of an inflammatory stimulus, respectively [6]. Blood coagulation disorders, including elevated D-dimer and lactate dehydrogenase levels, mild to no changes in prothrombin time (PT) and activated PTT, and increased antiphospholipid antibody levels, have been observed in COVID-19 infections [7, 8]. Thrombotic events are reported to occur in half of critically ill COVID-19 patients admitted to the intensive care unit and in 7.9% of hospitalized COVID-19 patients [9]. Several studies have demonstrated that COVID-19 predisposes individuals to thrombosis in both arteries and veins, with a risk of up to 25% for DVT, VTE, and PE. Pathological episodes, such as excessive inflammatory responses, DIC, immobility, and hypoxia resulting from significant lung injury, can contribute to VTE events [7, 10, 11].

Previous studies have shown that elevated CRP levels are associated with VTE in COVID-19 patients. Thus, given the association of elevated CRP levels with acute thrombotic episodes in the general population, CRP may serve as a useful marker for predicting TEEs in the context of COVID-19 [12]. In this retrospective study, we aimed to determine the association between CRP levels in patients with COVID-19 and the occurrence of TEEs.

Materials and Methods

This study was approved by the Ethics Committee of Kashan University of Medical Sciences, Kashan, Iran (ID: 3995; IR.KAUMS.MEDNT.REC.1403.026). This is a case-control study involving patients with COVID-19 who were hospitalized at Shahid Beheshti Hospital, Kashan, from 2019 to 2022. The sampling method used was simple random sampling. According to a study by Al-Samkari et al. [13], the mean (SD) initial CRP level in patients with TEEs was 114.43 (79.7), compared to 76.07 (84.2) in those without such events. With a 95% confidence interval and a test power of 80%, 71 individuals were selected for each group. Patient files scanned in the HIS system were selected based on the study's objective, and the necessary information was extracted. The diagnosis of COVID-19 was confirmed through positive PCR tests and clinical symptoms assessed by a specialist. All patients included in the study received treatment for COVID-19 according to national standard protocols. The diagnosis of TEEs was established through scintigraphy and CT angiography by a qualified specialist. A checklist was created to gather demographic information and clinical symptoms. After data collection, the information was transferred to SPSS version 26 software for statistical analysis.

Inclusion: criteria consisted of patients with a definitive diagnosis of COVID-19, aged between 18 and 75 years, suspected of having TEEs, who had undergone a CRP test with available results in their files, and who received standard national COVID-19 treatment. Exclusion: criteria included the absence of CRP levels in the patient's file, use of medications outside the standard national COVID-19 treatment protocol, underlying inflammatory diseases, previous TEEs, patients receiving anti-inflammatory treatments prior to contracting COVID-19, and insufficient information in the patient's file.

Results

Table 1 presents the demographic characteristics of both groups. The most common underlying conditions in both groups were hypertension, affecting 21 patients (30%), and diabetes, affecting 25 patients (35.7%). There were no significant differences between the two groups in terms of gender, age, or underlying conditions ($P > 0.05$).

The most common clinical symptom in the case group was shortness of breath, reported by 60 patients (85.7%). In the control group, cough was the most prevalent symptom, affecting 46 patients (65.7%). These findings indicate that the frequency of shortness of breath in the case group was significantly higher than in the control group ($P < 0.001$). There was no significant difference between the two groups

Table 1. Demographic characteristics [1].

Variables		Case group (n=70)	Control group (n=70)	*P* value [2]
Age (year)		55.13±14.74	55.14±13.44	0.90
Gender (%)	Male	39 (55.7)	38 (54.3)	0.86 †
	Female	31 (44.3)	32 (45.7)	
Underlying conditions (%)	Diabetes mellitus	15 (24.1)	25 (35.7)	0.65 †
	Hypertension	21 (30)	24 (34.3)	
	Hyperlipidemia	10 (14.3)	9 (12.9)	
	Cardiovascular	11 (15.7)	13 (18.6)	
	Pulmonary	8 (11.4)	7 (10)	
	Malignancy	5 (7.1)	2 (2.9)	

[1] Data are means ±SDs and percentages.
[2] Obtained from an independent t-test.
† Obtained from the Pearson Chi-square test.

Table 2. Comparison of clinical symptoms between the two groups [1].

Variables		Case group	Control group	*P* value [2]
Clinical symptom (%)	Fever	44 (62.9)	42 (60)	0.72
	Shortness of breath	60 (85.7)	41 (58.6)	<0.001
	Cough	36 (51.4)	46 (65.7)	0.08
	Gastrointestinal symptoms	24 (34.3)	16 (22.9)	0.13
	Coryza symptoms	9 (12.9)	5 (7.1)	0.26
	Myalgia	36 (51.4)	39 (55.7)	0.61
	Decreased level of consciousness	6 (8.6)	3 (4.3)	0.30

[1] The data are percentages.
[2] Obtained from the Pearson Chi-square test.

Table 3. Vital signs between the two groups [1].

Variables	Case group	Control group	*P* value [2]
Systolic blood pressure	120 (110-130)	120 (110-130)	0.78
Diastolic blood pressure	80 (70-80)	80 (70-80)	0.92
Number of breaths	18.5 (16-22)	17 (16-18)	0.002
Heart rate	95.5 (84.75-111.25)	87.5 (80-100.5)	0.01
SpO2	91 (86-95)	94 (88-96)	0.05

[1] Data are reported as median (first quartile-third quartile).
[2] Obtained from the Mann–Whitney U test.

Table 4. Comparison of inflammatory factors CRP and ESR [1].

Variables	Case group	Control group	*P* value [2]
CRP	67.5 (20-113)	30 (16.75-90)	0.03
ESR	36.5 (15.75-62.25)	37 (14.75-64.5)	0.74

[1] Data are reported as median (first quartile-third quartile).
[2] Obtained from the Mann–Whitney U test.

regarding clinical symptoms, including fever, cough, gastrointestinal symptoms, coryza, myalgia, and decreased level of consciousness ($p > 0.05$) (Table 2).

The two groups exhibited significant differences in respiratory rate (P=0.002) and heart rate (P=0.016), with patients having thromboembolic disorders showing higher rates than those in the control group. However, there were no significant differences in systolic and diastolic blood pressure or oxygen saturation (P>0.05) (Table 3).

On the other hand, the findings indicate a significant difference in CRP levels between the two groups (P = 0.03), with the median CRP level in the case group being higher than that in the control group. However, no significant difference was found in the comparison of ESR levels between the case and control groups

(Table 4).

Discussion

COVID-19 has a global mortality rate of approximately 2.2%. Given the significance of thromboembolic disorders and their potential cause of mortality, it is crucial to identify risk factors and markers that predict the occurrence of these events [14, 15]. Therefore, the present study aimed to investigate the association between baseline CRP levels and TEEs in patients with COVID-19.

Previous studies on patients with COVID-19 and thromboembolism have shown that most affected individuals are middle-aged [16]. In terms of gender, our patients were mostly middle-aged, with no gender difference. Supporting these results, a study conducted by Ortega found no significant association between thromboembolism and patient gender [17]. The most common underlying conditions among individuals with TEEs were hypertension and diabetes. A study by Yadollahi indicated that underlying conditions such as hypertension, heart attack, and stroke were associated with TEEs [18].

Based on the findings of this study, there was no significant difference between the two groups; shortness of breath was more common in patients with VTE. In this context, Garcia-Ortega et al. conducted a study aimed at determining the incidence, characteristics, and risk factors for pulmonary embolism (PE) among hospitalized patients with COVID-19, using a prospective observational design with a randomized patient group. The findings revealed that shortness of breath was a common symptom in patients with pulmonary embolism [16].

There was also a significant difference in CRP levels between the two groups, although no significant difference was observed in ESR levels. In a retrospective multicenter study conducted by Al-Samkari, the rate and severity of TEEs in hospitalized COVID-19 patients receiving standard-dose prophylactic anticoagulants were assessed. This study found that most patients with VTE had CRP levels > 100 mg/L, and CRP levels were higher in patients with thrombotic complications than in those without [13]. Another study highlighted a positive association between baseline hsCRP levels and subsequent VTE, indicating a 1.6-fold increased risk of VTE in those with the highest quintile of CRP compared to those with the lowest. Notably, the strongest association was found in subjects with a history of venous thrombosis within one year of blood sampling, suggesting that short-term inflammatory processes may directly stimulate the coagulation system [19]. In contrast, some studies have found no association between circulating CRP levels and VTE. For instance, Hald et al. reported no correlation between increased VTE and elevated CRP levels, particularly when excluding subjects with a history of previous VTE and those with hsCRP greater than 10 mg/L [20]. Conversely, another prospective study identified circulating CRP levels as an independent predictor of pulmonary embolism during COVID-19 [17]. Thus, while CRP appears useful in predicting VTE in the context of COVID-19, larger prospective studies are needed to confirm this association.

Our current understanding of the pathophysiology of thrombosis in COVID-19 emphasizes the significant roles of platelet activation, endothelial inflammation, and NETosis related to the infection [21]. Recent trials have indicated that antithrombotic therapies may improve outcomes for patients with COVID-19, albeit with an increased risk of bleeding [22, 23]. Therefore, novel approaches to target the harmful thromboinflammatory response associated with COVID-19 infection remain an urgent clinical need. On the other hand, it has been shown that increasing levels of vitamin D, HDL cholesterol, glutathione, and TAC reduces the risk of atherosclerotic cardiovascular disease over 10 years [24]. Therefore, in future studies, it is suggested that antioxidant supplements be used in clinical trials, which may have a positive effect on inflammatory factors such as CRP.

This study has several limitations. First, it was a retrospective analysis, which sometimes involved incomplete data, leading to the exclusion of patients with such data. Second, many factors influencing the occurrence of TEEs and certain laboratory findings, such as D-dimer levels, were not examined. Third, the tests utilized were not confined to a specific laboratory, and CRP levels at the time of admission were reported qualitatively in some cases.

Conclusion

Based on the findings of this study, patients with TEEs exhibited significantly higher levels of shortness of breath, heart rate, and respiratory rate compared to those in the control group. Additionally, we found that CRP levels were significantly elevated in patients with TEEs compared to the control group. This suggests that CRP can be a useful marker for identifying patients at risk.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Kashan University of Medical Sciences, Kashan, Iran (IR.KAUMS.MEDNT.REC.1403.026).

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Conflicts of Interest

The authors declared no conflict of interest.

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