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The effect of inflammatory markers on the CORADS degree and the effects of treatments on RT-PCR test results in COVID-19

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Abstract

Objective: There is still no diagnosis method with high sensitivity and specificity for COVID-19. Patient complaints, real-time reverse transcription-polymerase chain reaction (RT-PCR), inflammatory markers, clinical prognosis, and the degree of involvement in the chest CT, if necessary are evaluated in an effort to make a diagnosis. Delays in diagnosis have led to a rapid spread of the disease. This study aims to evaluate the effectiveness of the inflammatory markers and to determine the follow-up process of the patients by assessing the impact of the treatments administered on RT-PCR test results.

Material and methods: Files of 150 patients monitored in the wards with suspected COVID-19 are analyzed retrospectively. Patients were selected among those who underwent laboratory tests, RT-PCR testing and Thoracic CT within the first 24 hours of admission. Patients were divided into 5 groups based on the severity of involvement in Thoracic CT. Inflammatory markers were compared among the groups. Impact of the administered treatments on follow-up RT-PCR test results was evaluated.

Results: Studied inflammatory markers were in normal ranges and similar across all CORADS groups. Only the C-Reactive Protein (CRP) and Ferritin levels were showing an increase in accordance with CORADS severity. Mean time to testing negative on RT-PCR was 10 days across all treatment groups. Times to testing negative among patients receiving other treatments were similar.

Conclusion: Among the inflammatory markers, CRP and Ferritin values are correlated with CORADS severity. Administered COVID-19 treatments have similar impact on RT-PCR test results.

Key words: COVID-19, RT-PCR, coronavirus, CORADS

Introduction

Declared as a global health problem by World Health Organization (WHO), the novel coronavirus (COVID-19), SARS-CoV-2, emerged in Wuhan, China [1,2]. While COVID-19 may have an asymptomatic prognosis, it may also start with a dry cough, fever, severe headache, fatigue, rapidly progress to acute respiratory distress syndrome (ARDS) and therefore acute respiratory failure.

Leukocytosis, lymphopenia, thrombocytopenia, and high inflammatory markers negatively affect the process (IL-6, ferritin, ESR) [3,4]. The entire world is struggling to develop tests for rapid detection of the SARS-CoV-2 virus, to find the appropriate treatment for the infected people, and to control the spread of COVID-19 by developing a vaccine.

Quantitative reverse transcription-polymerase chain reaction (RT-PCR), thoracic CT scan, and inflammatory markers are used for virus detection, all

of which have unknown precision [5-7]. The sensitivity of RT-PCR testing is approximately 70-75% [8]. A negative test result does not rule out COVID-19 [9]. The latest studies claim that chest CT scanning detected the disease with high sensitivity even in RT-PCR negative patients [10]. A treatment model that could be considered effective is yet to be established. There are some medications currently administered, whose clinical trials are still underway for the prevention of viral replication and the damage caused by the disease [11].

During a pandemic, determining the etiological agent and immunological effects is the highest priority [12]. Changing characteristics of the pathogen since the beginning of the COVID-19 pandemic makes the diagnosis harder. In a pandemic, detecting and isolating the infected people and beginning treatment is the main rule in stopping the spread of the disease. In this paper, we aimed to evaluate the coherence of inflammatory markers and chest CT involvement, aside from RT-PCR and to determine the impact of the types of administered treatments on the RT-PCR test results [13].

Material and methods

This is a single-center, retrospective study involving 150 patients who were followed up and treated in Eskişehir City Hospital with suspected COVID-19 between May and August 2020. Admission criteria were fever, dyspnea, tachypnea, and poor general condition. Patients over 18 years of age, who were scanned with Thoracic Computed Tomography (CT) in the first 24 hours and diagnosed with 2019-nCoV disease according to the WHO's provisional guidelines, were randomly selected according to the order of admission. Those that were admitted to ICU upon worsening medical condition during the following-up and those who died were not included in the study. Peripheral blood samples and reverse transcription-polymerase chain reaction (RT-PCR) swab sample from oropharynx and nasopharynx were obtained from all patients at the time of admission. Patients' laboratory tests obtained at the time of admission, radiological images and medical records were analyzed retrospectively. Epidemiological, demographic, clinical, laboratory, management, and outcome data were obtained from the medical records of the patients. COVID-19 Lung Imaging Reporting and Data System (CORADS) developed by the Dutch Radiological Society was used in the classification of radiological images. CORADS is a scale that evaluates the severity of pulmonary involvement of COVID-19 from very low (CORADS 1) to very high (CORADS 5) [14].

Sociodemographic and categorical variables were expressed as frequency and percentage. Continuous variables were expressed using mean, standard deviation, median, minimum, and maximum values. Obtained results were expressed as means and standard deviations. Shapiro-Wilk test was utilized as the test of normality. An analysis of variances was used in order to evaluate the differences between groups and multiple comparisons were evaluated using the Kruskal-Wallis test. The value of $p<0.05$ was considered as statistically significant. IBM SPSS Statistics 25 software was used for the analysis.

Ethics

The study was approved by the relevant Institutional Review Board with the decision # 35 (Date: 29.09.2020). Written informed consent was obtained from the patient(s) or their legally authorized caregiver(s) for the publication of their anonymized information in this paper.

There was no person or institution financing the study. Relevant authors had full access to all data in the study and had final responsibility to submit for publication.

Results

150 patients admitted with clinically suspected COVID-19 were included in the study. Diagnosis of SARS-CoV-2 infection was verified with a positive real-time reverse transcription test (RT-PCR) result in 91 (60.7%) patients. RT-PCR tests were negative for 59 (39.3%) patients. Patients were divided into five groups according to the CORADS classification. Main characteristics of the study population according to the CORADS classification is shown in Table 1: In almost all CORADS groups, the number of male patients was higher. Only CORADS 5 group included more female patients. Mean age of the patients was 54.63±17 (p=0.064). The rate of testing negative in the first RT-PCR (RT-PCR 1) for the patients with CORADS 1 involvement was 71.4%. As the CORADS severity increased, the rate of testing negative in RT-PCR 1 test decreased. Positive RT-PCR 1 test result had a significant difference across all groups (p=0.020). CORADS 3 involvement in non-chronic disease was found to have the highest involvement and CORADS 5 involvement was the lowest. Presence of diabetes mellitus (DM) (%16), hypertension (%14), chronic obstructive pulmonary disease (COPD) (%5,3) and coronary artery disease (CAD) (%4,6) were found to be the comorbidities most frequently correlated with COVID-19. DM patients were the ones most often using Oral Antidiabetic Drugs, while hypertension patients were the ones most often using Angiotensin converting-enzyme inhibitors (ACEI) containing Calcium Channel Blockers (CCB) or Angiotensin Receptor Blockers (ARB). Inflammatory markers examined were within normal limits in all CORADS groups. In the CORADS 1 group, C-Reactive protein (CRP) and ferritin levels were found to be high even if there was no lung involvement. It showed a progressive increase as the severity of lung involvement increased. No distinctive feature was detected in the laboratory data of the patients, which were examined at the time of admission. This is shown in Table 2. Antiviral and various antibiotic treatments were administered to the patients according to the severity of their clinical condition. A second RT-PCR (RT-PCR 2) was obtained from those with improving clinical status after treatment initiation. 80 (87.9%) patients with a positive first RT-PCR result tested negative. 7 (11.7%) patients with a negative first RT-PCR result tested positive following the treatment. Those who received ceftriaxone and floxacin combination therapy became negative in 8 days, and those who received teicoplanin in 14 days. Those who received oseltamivir treatment became negative in 11 days, those who received Favipiravir treatment became negative in 10 days. Those who did not receive any treatment also became negative in an average of 10 days. The mean time to test negative was 10 days in all treatment groups. Times to test negative were similar among patients receiving other treatments. The types of treatment applied and the change in RT-PCR result according to the treatment are shown in Table 3.

Discussion

COVID-19 pandemic is still continuing all over the world with all its obscurities. Scientists are trying to reach a common consensus regarding diagnosis and treatment. However, the constantly evolving characteristics of the virus are making this harder. There is still no diagnosis method with high sensitivity and specificity for this disease. It is diagnosed based on patient

Table 1 Key Features of the Working groups

PATİENTS		CORADS1 n(%)	CORADS2 n(%)	CORADS3 n(%)	CORADS4 n(%)	CORADS5 n(%)	P Value
Age (year, Mean ±SD)		52±20	55±17	53±17	57±17	55±19	0,064
Sex	Male n(%)	15(%71,4)	22(%57,9)	29(%65,9)	16(%53,3)	7(%41,2)	0,301
	Female n(%)	6(%28,6)	16(%42,1)	15(%34,1)	14(%46,7)	10(%58,8)	
RT-PCR1 n(%)	positive	6(%28,6)	24(%63,2)	31(%70,5)	18(%60,0)	12(%70,6)	0,020
	negative	15(%71,4)	14(%36,8)	13(%29,5)	12(%40,0)	5(%29,4)	
RT-PCR2 n(%)	positive	2(%9,5)	2(%5,3)	4(%9,1)	5(%16,7)	5(%29,4)	0,107
	negative	19(%90,5)	36(%94,7)	40(%90,9)	25(%83,3)	12(%70,6)	
Co-morbidity n(%)	None	10(%47,6)	21(%55,3)	26(%59,1)	14(%46,7)	7(%41,2)	0,078
	Diabetes	2(%9,5)	9(%23,7)	4(%9,1)	8(%26,7)	1(%5,9)	
	Hypertension	5(%23,8)	5(%13,2)	7(%15,9)	1(%3,3)	4(%23,5)	
	Heart Diseas	0(%0,0)	1(%2,6)	4(%9,1)	1(%3,3)	1(%5,9)	
	Renal Failure	0(%0,0)	0(%0,0)	0(%0,0)	2(%6,7)	0(%0,0)	
	COPD*	2(%9,5)	1(%2,6)	1(%2,3)	1(%3,3)	3(%17,6)	
	ASTHMA	0(%0,0)	0(%0,0)	0(%0,0)	2(%6,7)	1(%5,9)	
	Thyroiditis	0(%0,0)	0(%0,0)	1(%2,3)	0(%0,0)	0(%0,0)	
	Epilepsy	0(%0,0)	1(%2,6)	1(%2,3)	1(%3,3)	0(%0,0)	
	Alzheimer's	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	0(%0,0)	
	Lung Cancer	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	0(%0,0)	
Diabetes Medicine n(%)	None Diabetes	19(%90,5)	29(%76,3)	41(%93,2)	22(%73,3)	15(%88,2)	0,120
	Oral Antidiabetic	2(%9,5)	8(%21,1)	3(%6,8)	8(%26,7)	1(%5,9)	
	İnsülin	0(%0,0)	1(%2,6)	0(%0,0)	0(%0,0)	1(%5,9)	
Hyperten-sion (HT) Medicine n(%)	None HT	14(%66,7)	26(%68,4)	34(%77,3)	22(%73,3)	13(%76,5)	0,354
	ACEI/ARB+			6(%13,6)	3(%10,0)	0(%0,0)	
	CCB**	2(%9,5)	8(%21,1)				
	ACEI/ARB	3(%14,3)	2(%5,3)	4(%9,1)	2(%6,7)	1(%5,9)	
	BETA-BLOKÖR	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	1(%5,9)	
	CCB	1(%4,8)	2(%0,0)	0(%0,0)	3(%10)	2(%11,8)	

ANOVA test was used to evaluate the comparison between groups.
* COPD: Chronic Obstructive Pulmonary Disease.
* * ACEI/ARB+CCB: Angiotensin Converting Enzyme İnhibitor/Angiotensin Receptor Blocker+ Calcium Channel Blocker

Table 2 Laboratory Characteristics of study groups

	CORADS				
	CORADS1 Mean ±SD	CORADS2 Mean ±SD	CORADS3 Mean ±SD	CORADS4 Mean ±SD	CORADS5 Mean ±SD
Glucose(mg/dL)	109 ±32	140 ±78	119±45	149 ±92	140 ±71
Serum Ürea Nitrogen(mg/dL)	13 ±4	15 ±7	17 ±8	18 ±11	19 ±11
Alanine Transaminase(u/L))	24 ±23	31 ±31	28 ±19	23 ±15	21 ±12
Aspartate Transaminase(u/L)	27 ±18	33 ±20	32 ±20	24 ±10	26 ±15
Lactate Dehydrogenase(mg/dL	185 ±41	208 ±83	217±93	200±75	213 ±60
White Blood Cell(WBC)(x109/L)	7,9 ±3,3	6,4 ±3,2	6,8±2,9	7,3 ±3,3	6,7 ±2,8
Absolute Neutrophil Count(x109/L)	5,2 ±2,5	4,2 ±2,4	4,7±2,7	5,2 ±3,2	4,9 ±2,4
Absolute Lymphocyte Count(x109/L)	1,6 ±0,6	1,5 ±1	1,4±0,6	1,5 ±0,7	1,3 ±0,5
Platelets (x109/L)	234 ±78	206 ±62	213±67	207 ±99	223 ±77
Neutrophil Lymphocyte Range	4,1 ±3,3	5,5±12,2	4,3±4,3	4,8 ±5,8	4,6 ±3,8
Platelets Lymphocyte Range	172,3±82,6	249,2±376,5	181,8±99,8	190,5±238,1	203,3 ±109,1
Hemoglobin (g/dL)	14,1 ±2	13,8 ±1,7	14,0 ±1,9	13,8 ±1,7	13,1 ±1,3
Hematocrit(g/ dL)	42,4 ±5,6	41,4 ±4,6	41,9 ±5,1	41,3 ±4,5	39,3 ±3,7
C-Reactive Protein(mg/ dL)	24,9 ±49,4	40,8 ±77,5	32,9±41,9	38,9 ±63,8	63,2 ±67,6
Troponin I(pg/ml)	6,2 ±6,7	10,4 ±11,8	10,6±17,2	7,1 ±7,3	4,4 ±7,4
Creatine kinase MB (CK-MB)(ng/ml)	2,1 ±3,5	1,9 ±2,4	1,3 ±1,1	7,1 ±7,3	4,4 ±7,4
D-dimer (mg/ml)	0,7 ±0,7	0,9 ±0,9	0,6 ±0,5	0,8 ±0,7	0,8 ±0,9
Ferritin(ng/ml)	236 ±379	241 ±232	261 ±186	284 ±161	274 ±236

* D-dimer results by coagulometric method.

Table 3 Types of treatment applied and RT-PCR change

		RT-PCR1		RT-PCR2		GÜN
		Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Mean
Chloroqui-ne n(%)	Not use	24(%26,4)	7(%11,9)	8(%44,4)	23(%17,4)	9
	Use	67(%73,6)	52(%88,1)	10(%55,6)	109(%82,6)	10
	P Value	0,032		0,008		
Azithromy-cin n(%)	Not use	47(%51,6)	26(%44,1)	12(%66,7)	61(%46,2)	9
	Use	44(%48,4)	33(%55,9)	6(%33,3)	71(%53,8)	10
	P Value	0,364		0,103		
Anti-viral Treatment n(%)	Not use	40(%44)	27(%45,8)	6(%33,3)	61(%46,2)	10
	Oseltamivir	13(%14,3)	25(%42,9)	4(%22,3)	34(%25,7)	11
	Favipiravir	38(%41,8)	7(%11,9)	8(%44,4)	37(%28)	10
	P Value	0,000	0,297			
Antibiotic Treatment n(%)	Not use	34(%37,4)	21(%35,6)	5(%27,8)	50(%37,9)	10
	Teicoplanin	2(%2,2)	1(%1,7)	0(%0,0)	3(%2,3)	14
	Ceftriaxone+ fourth-generation fluoroquinolone	5(%5,5)	5(%8,5)	0(%0,0)	10(%7,6)	8
	Ceftriaxone	26(%28,6)	24(%40,7)	4(%22,2)	46(%34,8)	10
	fourth-generation fluoroquinolone	24(%26,4)	8(%13,6)	9(%50)	23(%17,4)	10
	P Value	0,300		0,028		

complaints, RT-PCR test result, inflammatory markers, clinical prognosis and the degree of involvement in the chest CT, if necessary. Infection keeps spreading rapidly as diagnosis process is delayed. Lately, it has become very common to have chest CT in patients with negative RT-PCR test results but showing clinical symptoms of the disease. The question whether this should be among COVID-19 diagnosis criteria was brought to agenda in the scientific community. While sensitivity of Thoracic CT for COVID-19 varies between studies, most of these reported sensitivities are higher than those for RT-PCR testing [15, 16]. However, there are also studies stating that these studies involve suspected methodologies and need to be supported by larger studies [17]. Another issue regarding COVID-19 patients is that the process of transfer from pandemic wards to normal ward has not been standardized. This increases the occupancy rate in the hospital and brings a huge burden on the healthcare system. The aim in this study was to determine the relationship between inflammatory markers and severity of pulmonary involvement of the patient and the impact of the treatments administered on the RT-PCR test results.

In our study, we provide evidence for the correlation between CORADS severity and values of inflammatory markers CRP and Ferritin; it can be predicted that the pulmonary damage will exacerbate as CRP and Ferritin increase. The severity of lung involvement also negatively affects the prognosis of the patient. In this case, a more aggressive treatment approach and intensive care process come to the fore. Unfortunately, there is still no effective treatment for COVID-19. Various antibiotics, Favipiravir and Oseltamivir have been among the treatments tried since the onset of the disease. We evaluated these treatments for their effects on RT-PCR test results. Following the treatments administered at the hospital, RT-PCR test results became negative after average 10 days (min:8 days, max:14 days). Antiviral therapy or other treatments used did not affect test negative time. Based on this, we concluded that patients should be admitted to normal wards after a follow-up of at least 10 days in the COVID-19 wards and the insulation time should be for at least 10 days.

It was noted in many studies that high CRP, Ferritin and various inflammatory markers were correlated with severity of disease and poor outcomes [18]. In another research where a total of 21 studies were investigated, when those with severe disease and those without severe disease were compared, white blood cell count (WBC) was found to be significantly increased while lymphocyte and thrombocyte counts were decreased, and serum ferritin value was found to be significant for severe disease [19]. In our study, WBC, Absolute Lymphocyte Cell Count (ALC), Absolute Neutrophil Cell Count (ANC), thrombocytes, Neutrophil Lymphocyte Range (NLR), and Thrombocyte Lymphocyte Range (TLR) values were in normal ranges across all CORADS groups. Only CRP and ferritin values were increased proportionally to CORADS severity. Our patients were those that did not require ICU admission and were discharged from the wards with full recovery. In this case, it should be taken into consideration that in patients with mild disease inflammatory markers other than CRP and Ferritin may not increase even when CORADS severity is increased.

D-Dimer is correlated with clotting increase and thrombotic risk in COVID-19 [20]. D-dimer is a measure of clotting and fibrinolytic system and is used to evaluate the disease severity and plays an important role in risk stratification of patients for improving the clinical management. Increased D-dimer concentrations were associated with poor outcomes in COVID-19 [21]. In our study, D-Dimer was found to be in similar levels across all CORADS groups. Use of anticoagulants such as heparin and low molecular weight heparin (LMWH) in prophylactic treatment is important for limiting the increased clotting in COVID-19 patients [22-25].

In our study, patients admitted due to COVID-19 were given treatments intended for mitigating the viral replication of SARS-CoV-2 and alleviating the body's immune reaction. The treatments administered are shown in Table 3. Since the beginning of the pandemic, the treatments administered for COVID-19 have been questioned by experts, the importance of supportive care was emphasized.

In wards where patients are monitored, follow-up RT-PCR test results are taken into consideration. Based on the test results, patients continued to be isolated or transferred to another

ward. In this way, the spread of infection within the hospital was prevented.

In this respect, it can be thought that our study will contribute to the literature in terms of being a guide for clinicians. It is known that non-evidence-based treatments are used extensively in the treatment of COVID-19. The similarity of the effects of various treatments on RT-PCR test results suggested that treatment strategies should be re-evaluated.

In conclusion we think that our study acts as a guidance especially for the follow-up of patients who are relatively stable, do not have severe diseases, or do not require intensive care. Normal inflammatory biomarkers do not necessarily mean that there is no pulmonary involvement. Increased CRP and Ferritin values can be considered to indicate an increase in pulmonary involvement severity. The treatments administered had no impact on the follow-up RT-PCR test results; patients receiving different treatments became negative approximately 10 days later. This single-center study provides data to clinician on disease severity and patient coordination during the follow-up of ward patients.

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