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Evaluating the clinical, radiological, microbiological, biochemical parameters and the treatment response in COVID-19 pneumonia

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ABSTRACT

Aim: The coronavirus disease (COVID-19) has led to over 200,000,000 confirmed cases and over 4,250,000 confirmed deaths worldwide. The present study aimed to explore the links between epidemiological, clinical, biochemical, microbiological, and radiological data and treatment responses of inpatients with COVID-19 pneumonia.

Material and Method: The study included 131 patients hospitalized for COVID-19 pneumonia. Laboratory values such as complete blood count, coagulation profile, AST, LDH, sedimentation, CRP, BUN, creatinine, and D-dimer of the patients were analyzed. The diagnosis of COVID-19 was established by RT-PCR testing of respiratory tract samples. Thoracic CT images were used to determine the severity of involvement in patients. Statistical analyses were performed to establish the differences between the groups and the relationships between the variables.

Results: The most common comorbidities of the patients were hypertension (35.1%) and diabetes mellitus (24.5%). The patients with fever, cough, and dyspnea and who were PCR positive had the highest radiological involvement severity score. The involvement severity scores were negatively correlated with the lymphocyte count, lymphocyte percentage, and albumin levels ($p<0.05$). Concerning prognostic risk factors, the mean percentages of lymphocytes and eosinophils were significantly higher in the fully recovered patients than those in the intensive care unit ($p<0.05$).

Conclusion: Our study identified the percentages of lymphocytes and eosinophils as prognostic factors. Identifying the risk factors that predict the possibility of disease progression on admission may contribute to physicians' patient management, increase the therapeutic effect, and reduce the COVID-19 mortality rate.

Keywords: COVID-19, pneumonia, clinical parameters

INTRODUCTION

The coronavirus disease (COVID-19), which first appeared in China at the end of 2019, especially in Wuhan, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus (1,2). COVID-19, far from being a simple upper respiratory tract infection, has become an important and urgent public health problem worldwide in the form of a pneumonia pandemic (3).

Although the first transmission was believed to be from animal to human (bat-human), the human-to-human transmission caused the disease to become a pandemic (4,5), and the high infectivity of COVID-19 caused a rapid increase in new cases and a global outbreak (6,7). It caused over 200,000,000 confirmed cases and over 4,250,000 confirmed deaths worldwide (8). Studies so far show that the disease can result in very different clinical presentations, from asymptomatic to severe pneumonia that cause multi-organ and respiratory failure (9,10). Due to asymptomatic or mild cases, the disease spreads rapidly in the community (11).

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The first confirmed case of Turkey was identified on March 10, 2020, and the first confirmed death case due to COVID-19 occurred on March 17, 2020. Currently, patient diagnosis and treatment practices in our country are carried out based on the algorithms created according to the decisions of the Ministry of Health Scientific Committee (12) and updated in line with the international literature data (13). At present, agents such as lopinavir/ritonavir, favipiravir, and remdesivir are used to treat COVID-19 pneumonia, based on observational studies and in vitro evidence in Turkey and the world (14,15). However, none of these agents directly target SARS-CoV-2, and we need more scientific evidence on how much these agents benefit patients and their confidence intervals (16).

While the exact pathophysiological mechanism of COVID-19 is still largely unknown, there are ongoing studies on a therapeutic vaccine and a specific antiviral drug at full speed, and prophylactic vaccines are currently available. Until the discovery of effective treatment, sharing clinical experiences on COVID-19 pneumonia will contribute to the efficient use of medical resources, increase the therapeutic effect, and reduce mortality.

In our study, we plan to contribute to a better understanding of the pathogenesis of the disease and treatment algorithms by sharing the epidemiological, clinical, biochemical, microbiological, and radiological data and the treatment responses of our patients treated in the hospital for COVID-19 pneumonia.

MATERIAL AND METHOD

Our study was approved by the Ministry of Health (Document No: T00_56_55) and Çanakkale Onsekiz Mart University Rectorate Clinical Researches Ethics Committee (2011-KAEK-27/2020-E.2000063714). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Çanakkale Onsekiz Mart University Health Application and Research Hospital and Çan State Hospital were declared COVID-19 referral hospitals by our Ministry of Health on March 23, 2020.

Çanakkale Onsekiz Mart University Health Application and Research Hospital is a tertiary healthcare institution, and Çan State Hospital is a secondary healthcare institution. Both hospitals were reorganized to become an infectious disease center for the pandemic and only accepted COVID-19 patients referred by other healthcare institutions in Çanakkale province. The patients in our study were those admitted directly from the emergency department and treated in the Chest Diseases ward as inpatients with the diagnosis of COVID-19 pneumonia.

Patients and Methods

Electronic records, demographic, epidemiological, clinical, and imaging findings, treatments, complications, and outcomes of the patients treated in our ward with the diagnosis of COVID-19 pneumonia between March 27, 2020, and May 7, 2020, were collected from the Hospital Information System and analyzed retrospectively. The data collection was anonymous and patient consent was not obtained due to the retrospective nature of our study.

Inclusion criteria were being over 18 years of age and PCR positivity for COVID-19 with involvement on thoracic tomography scans compatible with COVID-19 pneumonia or PCR negativity for COVID-19 with involvement on clinical, contact information and thoracic tomography scans compatible with COVID-19 pneumonia. The exclusion criteria, in turn, were primary infection by other pathogens such as bacteria, fungi, etc.

Laboratory Findings

Laboratory values of the patients on admission were collected. The complete blood count, coagulation profile, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sedimentation, C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, and D-dimer values were analyzed.

Oxygen saturation was measured by pulse oximetry at rest on room air and confirmed by blood gas testing. Respiratory samples including combined nasopharyngeal swabs or sputum were sent.

Respiratory samples were used to confirm the diagnosis of COVID-19 by real-time reverse transcription-polymerase chain reaction (RT-PCR). Clinical samples were analyzed in BioRad CFX-96 real-time PCR machine using Bio-Speedy SARS-COV-2 RT-qPCR detection kit with primers for the RdRp (RNA-dependent RNA polymerase) region of the virus (Bioeksen, Turkey). For the PCR assay, samples were mixed with an equal volume of vNAT solution (Bioeksen, Turkey) and analyzed using the Bio-Speedy kit as per the manufacturer's recommendations. The result was interpreted as the presence of the viral RNA if the internal control human RNase P gene was positive in the sample. The threshold value for the samples was set at 200 RFU using BioRad CFX manager software and Cq values were calculated. Samples with low Cq values were considered to have a higher viral load.

Radiological Imaging:

Thoracic computed tomography (thoracic CT) was performed on the patients in the supine position with the end-inspiration breath-holding technique by scanning from the apex to the base of the lung, without intravenous contrast.

The thoracic CT images were evaluated in five categories using the data system for COVID-19 image reporting and grading (COVID-RADS) (17). The involvement severity groups were created by dividing both lungs into three zones as upper, middle, and lower for the severity of involvement. Volumetric involvement in each zone was calculated and summed.

Statistical Method

Data were transferred to the IBM SPSS Statistics 23 program. The study data were assessed using frequency distribution for categorical variables (number, percentage) and descriptive statistics for numerical variables (mean, standard deviation).

The difference between the two groups was examined by Independent Samples t-Test and the difference between more than two groups by One-Way ANOVA. Based on the ANOVA results, a Levene's test was performed to assess the homogeneity of variances, and a multiple comparison test (Bonferroni or Tamhane's T2) was performed to identify the group(s) causing a significant difference. Differences between the groups were analyzed by the Bonferroni test for variables with homogeneous variances and by Tamhane's T2 test for variables without homogeneous variances. A Chi-square test was used to analyze the relationship between two categorical variables and a Pearson's correlation test to examine the relationship between two numerical variables.

RESULTS

The study included 131 COVID-19 pneumonia cases diagnosed clinically/radiologically and treated in the hospital. 71 (54.2%) patients had PCR positivity for COVID-19 with involvement on thoracic tomography scans compatible with COVID-19 pneumonia and 60 (45.8%) patients had PCR negativity for COVID-19 with involvement on clinical, contact information and thoracic tomography scans compatible with COVID-19 pneumonia.The demographic findings of the study patients are presented in **Table 1.**

Four patients died in the Chest Diseases clinic. These patients aged from 77 to 90 years. The comorbidities of the non-surviving patients were chronic renal failure, hypertension, chronic heart failure, Lung cancer, and gastrointestinal malignancies.

Seven of the patients transferred to the Intensive Care Unit died in the intensive care unit. The comorbidities of the patients transferred to the intensive care unit were CRF, COPD, DM, malignancies, renal transplantation, and Alzheimer's.

Table 1. Distribution of Demographics

	N	%
Sex		
Male	74	56.4
Female	57	43.6
Age	63.35±16.41	
Place of admission		
Emergency department	84	64.1
Group 1 service	45	34.3
Intensive care unit	2	1.6
CT findings on admission		
Group 2: Compatible with Bacterial Infection	2	1.5
Group 3: Compatible with Viral Pneumonia	36	27.4
Group 4: Compatible with Mixed Infection	7	5.3
Group 5: Compatible with COVID-19	86	65.6
CORADS		
2	8	6.1
3	27	20.6
4	19	14.5
5	77	58.7
Involvement severity group		
2	62	47.3
3	37	28.2
4	27	20.6
5	5	3.8
GI symptoms		
Yes	5	3.9
No	126	96.1
Respiratory rate on admission	18.99±4.27	
Systolic Blood Pressure on admission	123.86±19.88	
Diastolic Blood Pressure on admission	75.68±10.29	
Pulse on admission	95.95±17.69	
Lymphopenia		
Yes	61	46.6
No	70	53.4
History of traveling abroad in the past 14 days		
Yes	2	1.6
No	129	98.4
Intubation		
Yes	16	12.2
No	115	87.8
Length of hospital stay	6.42±3.20	
Tomography on discharge		
Same	93	71.0
Progression	1	0.8
Regression	37	28.2
Discharge		
Non-survivor	4	3.1
Full Recovery	115	87.8
Intensive care unit	12	9.2

The most common comorbidities of the patients were hypertension (35.1%) and diabetes mellitus (24.5%). These were followed by cardiovascular diseases, pulmonary diseases, and neurological diseases, respectively. The distribution of comorbidities is presented in **Table 2.**

When the patients' presenting symptoms, the severity of radiological involvement, and the PCR result were evaluated together, the patients with fever, cough, and dyspnea who were PCR positive were found to have the highest radiological involvement severity score (**Table 3**).

The one-way ANOVA for the difference in SARS-CoV-2 RT-PCR Cq values between the involvement severity groups revealed no statistically significant difference ($p>0.05$).

Similarly, Pearson's correlation analysis did not show any statistically significant correlation between radiological involvement severity scores and Cq values ($p>0.05$) (**Table 4**).

The Pearson's correlation analysis for the association of the involvement severity scores with the lymphocyte count, lymphocyte percentage, and albumin values revealed a statistically significant negative correlation ($p<0.05$) (**Table 5**). The relationship between the lymphocyte count and radiological involvement severity score in diagnosed cases was assessed by Pearson's correlation analysis. There was a statistically significant negative correlation between involvement severity scores and lymphocyte counts ($p<0.05$).

In regards to prognostic risk factors, the independent samples t-test showed a statistically significant association between the percentages of lymphocytes and eosinophils, and the type of patient discharge ($p<0.05$). Accordingly, the mean percentages of lymphocytes and eosinophils were significantly higher in patients discharged with full recovery than in those staying in the intensive care unit (**Table 6**).

Table 2. Distribution of Comorbidities

	N	%
Comorbidities		
HT	33	35.1
DM	23	24.5
Cardiovascular diseases	21	22.3
Pulmonary diseases	20	21.3
Neurological diseases	17	18.1
Psychiatric disorders	9	9.6
Malignancies	6	6.4
Hypothyroidism	4	4.3
Kidney Diseases	4	4.3
Transplantation patients	2	2.1
Gastroenterological disorders	2	2.1

b: Independent samples t-tes

Table 4. The Radiological Involvement Severity and PCR Cq association

Involvement severity group	PCR Cq Mean±SD	Test/p
2	30.93±5.67	1.047/0.367A
3	34.08±4.45	
4	34.62±3.80	
5	33.33± 3.65	
Severity score	**CQ**	
r	0.298	
p	0.110	
N	30	

A: One-way ANOVA, r: Pearson's correlation coefficient, b: Independent samples t-test

Table 6. Prognostic risk factors

	Full Recovery	Intensive care unit	Test/p
	N (%)	N (%)	
Lymphocyte count	1.26±0.67	0.95±0.58	1.540/0.127b
Lymphocytes %	18.91±10.76	12.37±6.64	2.061/0.041b
Eosinophils %	1.16±1.42	0.25±0.36	4.904/0.000b
CRP	12.43±19.88	7.82±5.13	0.798/0.426b
Ferritin	365.11±713.81	570.27±483.75	-0.741/0.461b
Fibrinogen	451.85±135.6	411.86±131.24	0.735/0.465b
D-Dimer	588.23±1041.55	1001.78±1241.63	-0.92/0.360b
Troponin	47.08±81.06	217.69±340.15	-1.498/0.172b

n: Independent samples t-test, k: Chi-square test

Table 3. Assessment of the presenting symptoms, the severity of radiological involvement, and the PCR test result

		PCR Negative				PCR Positive				Total			
		Fever	Cough	Fever + cough	Fever + cough + dyspnea	Fever	Cough	Fever + cough	Fever + cough + dyspnea	Fever	Cough	Fever + cough	Fever + cough + dyspnea
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Involvement Severity group	2	2 (40%)	7 (46.7%)	3 (75%)	1 (33.3%)	2 (25%)	7 (53.8%)	5 (55.6%)	0 (0%)	4 (30.8%)	14 (50%)	8 (61.5%)	1 (25%)
	3	2 (40%)	2 (13.3%)	0 (0%)	2 (66.7%)	4 (50%)	6 (46.2%)	0 (0%)	0 (0%)	6 (46.2%)	8 (28.6%)	0 (0%)	2 (50%)
	4	1 (20%)	6 (40%)	1 (25%)	0 (0%)	2 (25%)	0 (0%)	3 (33.3%)	1 (100%)	3 (23.1%)	6 (21.4%)	4 (30.8%)	1 (25%)
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)
Severity score		7±4.45	7.53±5.83	6±6.68	6.67±4.51	8.75±3.41	5.54±3.1	7.33±5.85	15±4.87	8.08±3.59	6.61±4.79	6.92±5.87	8.75±5.56

Table 5. The Radiological Involvement and biochemical results association

		Severity Score			Severity Score			Severity Score
	r	-0.217		r	0.058		r	0.153
LYMPHOCYTE count	p	0.023	ALT	p	0.515	LDH	p	0.086
	N	110		N	129		N	128
	r	-0.211		r	0.099		r	-0.049
LYMPHOCYTES %	p	0.017	AST	p	0.268	CRP	p	0.588
	N	127		N	128		N	126
	r	0.009		r	-0.059		r	0.104
Respiratory rate	p	0.921	Urea	p	0.508	Procalcitonin	p	0.396
	N	129		N	129		N	69
	r	0.023		r	0.034		r	0.101
Total Leukocyte count	p	0.794	Creatinine	p	0.703	Sedimentation	p	0.371
	N	127		N	129		N	81
	r	0.076		r	-0.261		r	-0.149
Neutrophil count	p	0.428	Albumin	p	0.003	Troponin	p	0.221
	N	112		N	128		N	69
	r	0.098		r	0.179		r	0.102
Neutrophils %	p	0.271	Bilirubin	p	0.070	CK-MB	p	0.479
	N	129		N	103		N	50
	r	0.005		r	0.027		r	-0.042
Eosinophil count	p	0.956	Na	p	0.762	Ferritin	p	0.716
	N	108		N	129		N	78
	r	0.041		r	-0.145		r	0.054
Eosinophils %	p	0.670	K	p	0.104	D-DIMER	p	0.639
	N	108		N	128		N	77
	r	-0.046		r	-0.122		r	-0.130
PLATELETS	p	0.604	Cl	p	0.641	Fibrinogen	p	0.308
	N	129		N	17		N	63

r: Pearson's correlation coefficient

DISCUSSION

The patients we followed up in the Chest Diseases ward of Çanakkale Onsekiz Mart University Medical Faculty Hospital and Çan State Hospital were referred to us from the surrounding districts and villages due to COVID-19 pneumonia and respiratory failure. Therefore, our study patients were older than the China-based cohorts, with a mean age of 63.35 + 16.41 years, and had more comorbidities (100%) (18-20). However, the mean age of our patients was similar to that of the patients in the COVID-19 studies conducted in the European and American populations (21,22). In our study, male patients accounted for 56.4% of the study sample. This rate was similar to those reported by the studies from China (58%), Italy (60%), and New York (56%) (19,23,24).

In our study, the leading comorbidities of the patients followed up with COVID-19 pneumonia were hypertension (HT) (35.1%) and diabetes mellitus (DM) (24.5%), which were followed by cardiovascular diseases, pulmonary diseases, and neurological diseases, respectively. Our results were in line with the results of a meta-analysis involving a systematic literature review that concluded a high prevalence of hypertension and diabetes among comorbidities in patients with COVID-19 (25). The results of another systematic literature review and meta-analysis study, in agreement with our study, also showed that the most common comorbidity among patients with confirmed COVID-19 infection was HT, followed by cardiovascular diseases and diabetes, and concluded that it was associated with significant morbidity in patients with chronic diseases (26). A meta-analysis study by Sanyaolu et al. (27) found that 88.8% and 68% of COVID-19 patients had fever and cough, respectively. In our study, 73% of the patients had a fever and 67% had a cough. The same study examined comorbidities associated with COVID-19, observing that COVID-19 had a more severe course in older adult patients, and identifying the comorbidities associated with COVID-19 as hypertension (15.8%), cardiovascular diseases (11.7%), and diabetes mellitus (9.4%) . Another study examined the biopsy results of 26 patients who died after SARS-CoV-2 infection. Accordingly, 65.4% of the patients had arterial hypertension, 38.5% had obesity, 34.6% had chronic ischemic heart disease, and 15.4% had Type 2 diabetes. The autopsy results showed that 92.3% of the patients had coronary artery disease (28). The study by Cummings et al. (29) with data on 1150 hospitalized COVID-19 patients reported that older age, chronic

heart disease, and high concentrations of D-Dimer were associated with mortality. These studies and our study show that comorbidities such as hypertension, cardiovascular diseases, and DM are particularly common in COVID-19 patients and negatively affect the course of the disease.

Studies have demonstrated that the disease progresses more severely and mortality is higher in COVID-19 patients with diabetes. It has been shown that COVID-19 patients with diabetes but without any other comorbidity are at greater risk of severe disease when assessed by organ injury, inflammatory factors, and hypercoagulation (30). In two different clinical trials conducted in the USA with COVID-19 patients admitted to the ICU, the rate of diabetes mellitus was found to be 58% and 33%. This may be related to glucotoxicity resulting from impaired glucose metabolism in patients with diabetes mellitus, and endothelial injury resulting from overreacting inflammatory responses (31,32). In our study, diabetes mellitus was detected in 24.5% of the COVID-19 patients and was a common comorbidity.

The four patients who died in our clinic had a higher mean age than other patients and had CRF, HT, CHF, lung cancer, and GI malignancies as comorbidities. The comorbidities identified in the patients with a deteriorating condition while receiving treatment in our clinic and thus were transferred to the intensive care unit were CRF, COPD, DM, malignancies, renal transplantation, and Alzheimer's disease. Seven of the patients transferred to the intensive care unit died in the intensive care unit. The rate of transfer to the intensive care unit was 9.2%, and the overall mortality, including the patients transferred to the intensive care unit, was 8.4% in our study. A study conducted to examine mortality rates in the USA in 2020 with 20736 patients compared the mortality rates on admission from March 2020 to November 2020 and determined that the mortality rate was 19.1% between March and April 2020 while decreasing to 10.8% between September and November 2020 (33).

A retrospective study of 1057 patients showed that PCR Ct values, which indicate the viral load, were not associated with patients' need for oxygenation (34). This finding is similar to our finding indicating no correlation between PCR Ct values and radiological findings. However, our study, when evaluating the patients' presenting symptoms, the severity of radiological involvement, and the PCR result together, found that the patients with fever, cough, and dyspnea who were PCR positive had the highest radiological involvement severity score. This suggests that a higher rate of positive PCR tests may be detected in symptomatic patients.

In our study, we observed that the count and percentage of lymphocytes on hospital admission were negatively correlated with radiological involvement in COVID-19 patients. We also identified the lymphocyte percentage as a prognostic factor in COVID-19 patients, and we observed that patients with a high lymphocyte percentage had a lower risk of admission to the ICU. In the early months of the outbreak, Guan et al. (19) described the clinical characteristics of 1,099 patients with laboratory-confirmed COVID-19 from 552 hospitals in China until January 29, 2020. Lymphopenia was detected in 82.1% of patients, and leukocyte/lymphocyte counts in the blood and the chest X-ray/CT findings were found to be associated with poor clinical outcomes. Similarly, Wagner et al. (35) reported that a low lymphocyte count and lymphopenia were more common in COVID-19 patients admitted to the ICU than in non-admitted patients. The same study also observed more common acute kidney injury in COVID-19 patients with lymphopenia. Another study with 306 patients found a low lymphocyte count (< 790/mm^3) to be associated with mortality and the need for mechanical ventilation (36). Various mechanisms have been proposed for the occurrence of lymphopenia in COVID-19 patients. It is believed that cytokines such as TNF-alpha and IL-6 produced in the cytokine storm seen in COVID-19 patients cause the death of considerable lymphocytes by apoptosis in lymphoid organs. In addition, an increase has been observed in receptors such as PD-1, which leads to the depletion of T lymphocytes, in the cell membranes of T lymphocytes in COVID-19 patients (37). Lymphopenia and low T lymphocyte counts have almost always been observed in severe COVID-19. When these findings are evaluated together, lymphocyte percentage on hospital admission appears to be an important prognostic factor.

Our study also identified the percentage of eosinophils as a prognostic factor in COVID-19 patients, as is the case with the percentage of lymphocytes, and observed that patients with a high percentage of eosinophils had a lower risk of admission to the intensive care unit. Similarly, a study of 97 COVID-19 patients found that patients with low eosinophil counts on hospital admission had more severe symptoms, more lesions in the lung, and longer hospital stays (38). Another study with 190 patients, in turn, observed that the eosinophil count was lower in the critically ill COVID-19 patients than those with mild and severe COVID-19, and showed that a decrease in eosinophil count was associated with mortality (39).

A study of 189 patients investigating albumin levels in COVID-19 patients found that patients with high albumin levels on hospital admission had a lower risk of acute respiratory distress syndrome and ICU admission (40). A study involving 299 patients showed

an association between a low albumin level and mortality in COVID-19 patients. It is believed that the low albumin levels of these patients may result from severe systemic inflammation (41). According to our data, there was a negative correlation between the albumin level and the severity of radiological involvement.

Our study has some limitations. First, the sample size was small, including patients only from two centers in Çan Province. Studies that include more patients and centers may be needed. Adding other specific markers to our study may further increase sensitivity and specificity. Antiviral agents and corticosteroid use were not included as variables in this study. It would not be healthy to generalize without supporting the data obtained in this study with more comprehensive studies; however, the results of our study seem to be consistent with the current literature.

CONCLUSION

Increasing numbers of cases and clinical experience have led to more detailed information about COVID-19 pneumonia. Our study identified the percentages of lymphocytes and eosinophils as prognostic factors. It would be useful to clarify independent high-risk factors and accurately estimate the progression of COVID-19 by multivariate analysis. Therefore, identifying risk factors that predict the possibility of disease progression on admission would help physicians to decide which patient groups can be safely managed in district hospitals and who should be transferred early to tertiary care centers. This may allow the efficient use of medical resources, improve the therapeutic effect, and reduce the COVID-19 mortality rate. The predictions of prognostic factors in this study would help guide ongoing response efforts, as well as provide accurate and efficient healthcare resources needed in times of sudden rises of cases

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Ministry of Health (Document No: T00_56_55) and Çanakkale Onsekiz Mart University Rectorate Clinical Researches Ethics Committee (2011-KAEK-27/2020-E.2000063714).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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