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The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

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The Medical Bulletin of Haseki

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Evaluation of the Prognostic Utility of Computed Tomography New Severity Score in COVID-19 Pneumonia Patients

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Abstract

Aim: To investigate the relationship between infection markers (lymphocyte, C-reactive protein, and D-dimer) at the time of diagnosis, and the new scoring system created according to the amount and pattern of pneumonic involvement in recent computed tomography (CT) of patients with Coronavirus disease-2019 (COVID-19) pneumonia

Methods: We investigated retrospectively patients diagnosed with COVID-19 with positive reverse transcriptase-polymerase chain reaction on throat swabs between March 17 and May 1, 2020. Eighty-nine cases with COVID-19 pneumonia were divided into two groups according to the level of poor prognostic criteria (blood lymphocyte count <800/µL or C-reactive protein >10x upper limit of normal value or D-dimer >1000 ng/mL). The severity of pulmonary parenchymal findings was scored using two separate scoring systems previously as well as a third separate scoring system, namely the "modified CT severity scoring". The cut-off point for severe infection was investigated by comparing the scores of the groups with and without severe infection.

Results: All three scoring systems were significantly higher in the group with severe infection compared to those without severe infections. A modified CT score above 3.4 accompanies at least one of the poor prognosis findings (sensitivity 77.6%, specificity 61%).

Conclusion: In patients with COVID-19 pneumonia, the presence of at least one of the infection markers that are poor prognosis markers at the time of diagnosis indicate that the modified CT severity score of pneumonia will be above 3.4.

Keywords: COVID-19, pneumonia, tomography, X-ray computed, lymphocyte count, fibrin fragment D, C-reactive protein

Introduction

The diagnosis of Coronavirus disease-2019 (COVID-19) pneumonia, which is a viral infection, is made by the positivity of the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test. Since pneumonia findings on computed tomography (CT) can sometimes appear before RT-PCR positivity in the literature, radiology has become important in the diagnosis (1,2), and initiatives have been undertaken to establish a common reporting language to make CT findings easier to understand by the clinicians (3-5). All of these CT findings, which can be classified as ground-glass opacities, cobblestones, and consolidation were written descriptions of CT images of COVID pneumonia (6,7).

While at the beginning of the pandemic CT reporting of COVID-19 pneumonia findings was in the form of describing findings, over time, requests began to be made to determine the amount of parenchymal involvement to have an idea about the severity of the disease. In line with similar studies published during the pandemic, we thought that in the evaluation of patients with COVID-19 pneumonia, the pattern and amount of involvement in the lung parenchyma became important CT findings. Especially, if a relationship could be shown between these CT findings and laboratory findings, the

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clinician could then predict the severity of pneumonia to be encountered in CT, even if CT examination was not performed at certain laboratory values. Therefore, in our study, we developed a new scoring system based on the amount of CT involvement as well as the involvement pattern (affecting the weight of parameters) and aimed to investigate the relationship between this scoring system and inflammatory markers used by the Ministry of Health as poor prognostic factors. Thus, we planned to show how accurately the poor prognostic factors in the laboratory values of the patient at the time of CT can be identified with this CT scoring system and to provide the clinician with an idea about the severity of pneumonia with these laboratory findings at the time of seeing the patient.

Methods

Study Design

This single-center, a retrospective cross-sectional study was conducted with patients who were diagnosed with COVID-19 pneumonia in a training and research hospital between March and June 2020 after receiving approval from a local ethical committee.

Study Population

Before starting the study, approval was obtained from the Ethics Committee of Kecioren Training and Research Hospital (10.6.2020/2116). Among the patients diagnosed with COVID-19 with positive RT-PCR test performed on throat swabs between March 17 and May 1, 2020, in our hospital, 89 (male/female: 44/45) patients with typical findings of COVID-19 pneumonia according to the American College of Radiology (ACR) guidelines but did not have any other signs of disease affecting the lung (such as AC malignancy, lobectomy, or tuberculosis) were included in the study. The study was retrospective, so an informed consent form was not applicable.

Neutrophil count, lymphocyte count, serum C-reactive protein value, and D-dimer value were recorded from the examination performed within 24 hours of the CT scan dates of the patients by an infectious diseases expert who was blinded to the CT findings. Patients were divided into two groups as those with severe infection and those without, according to whether they exhibited poor prognostic criteria specified in the Ministry of Health guideline (Blood lymphocyte count <800/μL or C-reactive protein >10x the upper limit of normal value or D-dimer >1000 ng/mL) (8). The CT findings and scores described below were compared between these two groups of patients.

Computed Tomography

All CT examinations were performed by a multi-slice CT device with 16 detectors (Siemens Somatom Emotion 16, Siemens) using automatic dose modulation technique and the same acquisition protocol. Intravenous contrast material was not used in the examination. While in the supine position, the patient was instructed to hold his breath at the end of inspiration, and the examination area was adjusted from the lung apex to the end of the costophrenic angle. CT settings were as follows: 120 kVp, 1.35:1 pitch, reconstruction matrix 512x512, high-spatial-resolution algorithm, and 1 mm section thickness. Images were analyzed in three planes using the multiformat imaging technique.

Computed Tomography Evaluation

All CT images were retrospectively evaluated in the lung window (WW: 1500 HU, WL: -500 HU) by two expert radiologists (OG; CO) with 13 and 12 years of experience in thoracic radiology. Lung parenchymal involvement findings were named according to the definitions in the ACR guideline (4). The severity of pulmonary parenchymal findings was scored using two separate scoring systems previously described in the literature (9,10), as well as a third separate scoring system, namely the "modified CT severity scoring" defined below. There was a two-week gap between the evaluations made with these three separate scoring systems. These scoring systems were as follows:

1. CT score: Developed by Pan et al. (9), this scoring was made according to the percentage of involvement in each lobe. The scores obtained for each lobe (0=absent, 1=1-5% involvement rate, 2=6-25% involvement rate, 3=26-50% involvement rate, 4=51-75% involvement rate, 5=>75% involvement rate) were summed up to obtain the "total lung involvement score". In this system, the minimum and the maximum score for each case were 0 and 25, respectively [5 (lobe) x5 (involvement rate)].

2. CT severity score: This scoring system was developed by Huang et al. (10). In this system, a score was obtained for each lobe (0=absent, 1=1-5% involvement rate, 2=6-25% involvement rate, 3=26-50% involvement rate, 4=51-75% involvement rate, 5=>75% involvement rate) and then "1" was added to this score if cobblestone appearance was present or "2" was added to this score if consolidation was present in one lobe. The "total lung involvement score" was found by summing the scores of all lobes. In this system, the minimum and maximum scores for each case were determined as 0 and 35 [5 (lobe) x5 (involvement ratio) + weight coefficient].

3. Modified CT severity score: 18 lung segments in total in two lungs were divided into 20 regions. The left lung apicoposterior segment was divided into apical and posterior regions, and the left lung anteromedial basal segment was divided into anterior and mediobasal segments. The involvement rates were initially examined

for the findings in each region (0=absent, 1=1-49% involvement rate, 2=50-100% involvement rate). Parenchymal findings in each region were divided into five according to ground-glass opacities, a cobblestone appearance, mixed type with predominantly ground-glass opacities, mixed type with predominantly consolidation, and pure consolidation. Among these parenchymal findings, involvement coefficients were formed by separating the "involvement feature" into further groups (ground-glass opacities "0.2"; cobblestone appearance "0.4"; mixed type with predominantly ground glass opacities "0.6", mixed type with predominantly consolidation "0.8" and pure consolidation "1"). The involvement score of each region was obtained by multiplying the involvement coefficient and ratio for each region. The sum of the involvement scores of the 20 regions gave the "total lung involvement score". In this system, the minimum and the maximum score for each case was determined as 0 and 40 [20 regions x^2 (involvement ratio) x1 (involvement feature)].

Statistical Analysis

All data were analyzed by IBM SPSS Statistics for Mac, version 25.0 for Mac OS X (IBM Corp., Armonk, N.Y., USA). The categorical values of the patients were expressed as a number and a percentage and were analyzed with a chi-square test. Whether the numerical variables were normally distributed or not was evaluated with the Shapiro-Wilk test, histogram, and Q-Q plots. While normally distributed numeric variables were presented as a mean and standard deviation, non-parametric variables were presented as median values and an interquartile range (IQR) of 25%-75%. The non-parametric values were analyzed using the Mann-Whitney U, and the parametric ones with a Student's t-test. To assess the prognostic utility of CT scores at varying cut-off values for the distinction between the severe and non-severe infection groups, a receiver-operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated (Figure 1). The best of cut-off values was decided by using Youden's index. The 95% confidence intervals (95% CIs) were calculated whenever appropriate, and a two-tailed $p<0.05$ was considered statistically significant.

Results

The mean age of patients was 49±14.2 and 44 (49.2%) of them were male. Thirty (33.7%) patients were categorized in the severe infection group and fifty-nine (66.3%) of them were categorized with the non-severe infection group according to laboratory examination. In comparing CT findings and CT scores of both groups, it was found that all CT score points were higher in the severe infection group than the non-severe infection group ($p<0.05$). All CT scores and laboratory results were presented in Table 1.

To assess the prognostic utility of all CT scores at varying cut-off values for the distinction between the severe and non-severe infection groups, a ROC curve was generated, and the AUC was calculated. Accordingly, the AUC values of CT score, CT severity score and modified CT severity score 0.711 (95% CI: 0.592 to 0.830), 0.684 (95% CI: 0.564 to 0.804) and 0.722 (95% CI: 0.615 to 0.829), respectively. The best cut-off value of all CT scores for distinguishing between the severe and non-severe infection groups and the sensitivity/specificity values for this cut-off level were presented in Table 2. Also, for modified CT score,

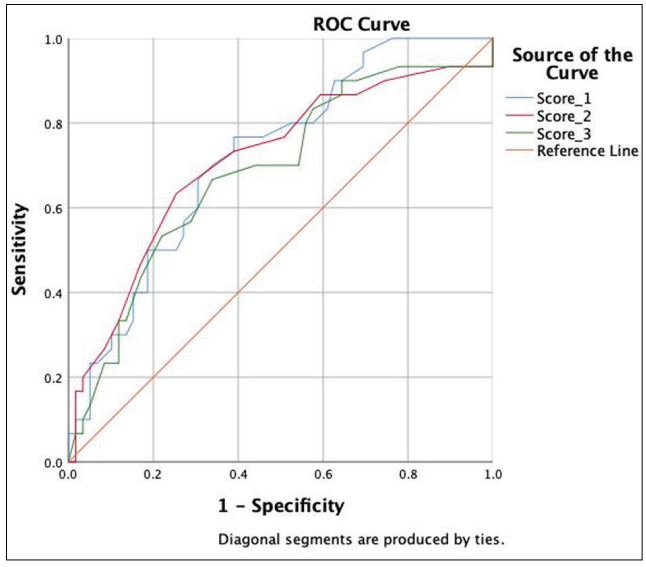

Figure 1. ROC analysis data
ROC: Receiver-operating characteristic

Table 1. CT scores and laboratory findings on the admission of all patients with confirmed COVID-19 pneumonia according to severe and non-severe groups

Final CT scores	Non-Severe n=59	Severe n=30	p
CT score	7 (3 to 9)	9 (6.75 to 12)	0.001
CT severity score	11 (5 to 14)	15 (10 to 18.75)	0.005
Modified CT severity score	3 (1.4 to 5.4)	5.5 (3.3 to 8.7)	0.001
Laboratory findings on admission median (IQR 25-75%)			
Neutrophil	3470 (2810 to 4160)	4150 (3345 to 5165)	0.013
Lymphocyte	1720 (1320 to 2220)	1090 (740 to 1705)	<0.001
D-dimer	370 (280 to 540)	680 (330 to 1580)	0.003
C-reactive protein	8.3 (3.9 to 19)	35.6 (7.25 to 65.7)	<0.001

COVID-19: Coronavirus disease-2019, CT: Computed tomography, IQR: Interquartile range

diagnostic performance values and Youden's index scores for different cut-off points were presented in Table 3. According to this, 3.4 points were considered as a cut-off, sensitivity/specificity values of modified CT severity score for the diagnosis of severe COVID-19 pneumonia were as follows; 76.7 (95% CI: 57.72 to 90.07) and 61 (95% CI: 47.44 to 73.45), respectively.

Discussion

Even though it feels like COVID-19 has been in our personal lives for a lifetime, COVID-19 is an infection that we have been faced with for a short time scientifically and therefore a lot about it is still unknown. Although certain progress has been made in terms of diagnosis, patient management and treatment strategies vary. Since it is a pandemic, the fact that many people are infected at the same time has made patient management more important. In Turkey, treatment and patient management are standardized according to the guidelines set by the Ministry of Health (8). In the present study, we found that in cases where at least one of the poor prognostic markers specified in this guideline was high (high C-reactive protein, high D-dimer, and lymphopenia), the "modified CT severity score" was also high (p<0.01).

Different laboratory data were used in studies trying to predict clinical severity in COVID-19 patients. As in our study, "CT score," which is the first scoring system we used in this article, was used in the study conducted by Li et al. (11) with 90 patients, comparing patients based on infection markers. In this study, CT and C-reactive protein value were higher and lymphocyte count was lower in patients with a severe condition (meeting at least one of the following conditions: respiratory rate 30 times/min, O_2 saturation ≤93%, $(PaO_2)/(FiO_2)$ ≤300, need for mechanical intubation, shock, and organ failure) (p<0.001). Francone et al. (12) used the same scoring system and found a statistically significant positive correlation between the CT score and C-reactive protein (r=0.6204, p<0.0001) and D-dimer (r=0.6625, p<0.0001). In the present study, in all three scoring systems used in parallel with these findings, we found that the scores were higher in terms of infection parameters in the presence of poor prognosis, and the most significant results were obtained with the "modified CT score" system (p<0.001).

It was understood that lung involvement was the basis of the events affecting the poor prognosis of the patients during the pandemic. During the SARS epidemic, Chang et al. (13) showed that beyond the presence of lung involvement, the amount of involvement in viral infections was also important in patient management (13). Based on this scoring system, Pan et al. (9) created the "CT score" that takes into account the involvement rates in the lungs (0-5-25-50-75-100%) of patients with COVID-19 pneumonia. In this study involving 21 cases, patients were divided into 4 stages according to the time between symptom onset and CT scan, and CT score was found to be higher in those with a longer-term disease history [stage 1 (0-4 days) CT score 2±2, stage 2 (5-8 days) CT score 6±4, stage 3 (9-13 days) CT score 7±4, stage 4 (>14 days) CT score 6±4]. In the same study, the most common finding was ground-glass opacity for stages 1 and 2, and consolidation for stages 3 and 4. In the present study, we

Table 2. The prognostic values of all CT scores to the prediction of severe infection in patients with diagnosed COVID-19 pneumonia

Variables	CT score	CT severity score	Modified CT severity score
AUC (95% CI)	0.711 (0.592 to 0.830)	0.684 (0.564 to 0.804)	0.722 (0.615 to 0.829)
Best cut-off value*	9	13	3.4
Sensitivity (95% CI)	63.33 (43.86 to 80.07)	66.67 (47.19 to 82.71)	76.7 (57.72 to 90.07)
Specificity (95% CI)	74.58 (61.56 to 85.02)	66.1 (52.61 to 77.92)	61 (47.44 to 73.45)
PLR (95% CI)	2.49 (1.49 to 4.17)	1.97 (1.27 to 3.05)	1.97 (1.35 to 2.87)
NLR (95% CI)	0.49 (0.3 to 0.8)	0.5 (0.29 to 0.86)	0.38 (0.19 to 0.75)
Accuracy (95% CI)	70.79 (60.19 to 79.95)	66.29 (55.49 to 75.97)	66.29 (55.49 to 75.97)

*The best of cut-off values was decided by using Youden's index. AUC: Area under curve, PLR: Positive likelihood ratio NLR: Negative likelihood ratio, COVID-19: Coronavirus disease-2019, CT: Computed tomography, IQR: Interquartile range, CI: Confidence intervals

Table 3. The sensitivity and specificity values for different cut-off points of modified CT severity score

Modified CT score	Sensitivity (%)	Specificity (%)	NLR	PLR	Accuracy	Youden's index
2	90 (73 to 97)	35 (23 to 49)	0.28 (0.09 to 0.86)	1.4 (1.1 to 1.75)	53 (43 to 64)	0.255
3	80 (61 to 92)	47 (34 to 60)	0.42 (0.2 to 0.9)	1.5 (1.1 to 2.05)	58 (47 to 68)	0.274
3.4	76 (57 to 90)	61 (47 to 73)	0.38 (0.19 to 0.75)	1.9 (1.35 to 2.8)	66 (55 to 75)	0.376
5	53 (34 to 71)	72 (59 to 83)	0.64 (0.42 to 0.97)	1.9 (1.1 to 3.3)	66 (55 to 75)	0.262
6	50 (31 to 68)	81 (69 to 90)	0.61 (0.42 to 0.89)	2.6 (1.4 to 5.09)	70 (60 to 79)	0.313

PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, CT: Computed tomography

found that all scoring systems, including the CT score, were successful in detecting severe infection (p<0.001).

We stated that we named the systems in the literature in which the involvement pattern is also included in the scoring as "CT severity score". Using the "CT severity score", Yuan et al. (14) conducted a study with 27 patients (a coefficient of 2 for ground glass and 3 for consolidation was used) and found that the median CT score of the cases that resulted in mortality was higher than the surviving group [(30 (IQR) 7-13) vs 12 (IQR 11-43), p=0.021]. This study, unlike many other studies, divided the lungs into only three zones. In the present study, we divided and evaluated the lung in 20 regions, ensuring that the evaluation included as complete information on the lung as possible, and included 5 different involvement categories into the evaluation, enabling the severity of infection to be included in the scoring according to the histopathological response in the patient.

The basis of this was that the findings we saw on CT showed different processes histopathologically. Ground glass appearance is defined as images caused by pulmonary edema and hyaline membrane formation, cobblestone appearance is defined as images caused by alveolar edema and interstitial inflammation, and consolidation is defined as images caused by cellular fibromyxoid exudate accumulation in the alveoli (1,15). We have created a formula in which the area of involvement in each lung area is more effective, but the pattern of this involvement is also considered. While the mean score was 3 (1.4-5.4) in our non-severe patient group, the mean score was 5.5 (3.3-8.7) in the severe group, and the difference between the groups was significant (p<0.001). We think that the reason for the relatively low scores in our patient groups is that the patients presented at an early stage and time of their complaints. Since we aim to show the relationship between infection markers at the time of diagnosis and a recent CT score, the low maximum score indicates that the participants were in the early period of the disease.

We determined that this scoring system, in which histopathological information has been added to the CT information with the created "modified CT severity score", was better correlated with the elevation in at least one of the infection markers, which were defined as poor prognosis indicators in the literature, compared with the other scoring systems described previously (Table 2). Accordingly, considering the cut-off point obtained with the modified CT score, this cut-off value can be used as a support parameter to indicate poor prognosis of the disease, or if the specified limits are exceeded ven in one of the parameters such as lymphocyte, C-reactive protein, and D-dimer that can be checked in many countries around the world, time of the CT scan can be changed with the prediction that the patient's pneumonia may be acute or this information can support disease management in cases where CT cannot be performed.

Study Limitations

There are certain limitations of this study. Clinical outcome was not evaluated in our study. It is known that clinical outcome is the result of multiple factors such as age, comorbidity, time of treatment initiation, and the applied treatment protocol (14,16-20). The objective of this study was to evaluate the correlation of CT findings at the time of diagnosis with the laboratory values obtained at the same time and to support the clinician's management of newly diagnosed patients for COVID-19 pneumonia based on our inferences. Another limitation is that the number of patients in our study was 89, but statistical significance could be detected for scoring. There is a need for further studies involving larger patient groups to validate our findings obtained with the modified CT score. Another limitation may be the lack of artificial intelligence used to evaluate CT in this study. However, we tried to establish a scoring system that can be used all over the world during a pandemic, and we thought that it would best that this scoring system did not rely on high-priced technology.

Conclusion

If there is at least one of the poor prognosis findings (high C-reactive protein, high D-dimer, and lymphopenia) in the infection markers of cases with COVID-19 pneumonia, pneumonia will accompany on CT with a modified CT score above 3.4 (sensitivity 76%, specificity 61%). For this reason, these markers exceeding the specified limits should make the clinician think that pneumonic infiltration becomes prominent on CT (hence the modified CT severity score increases). We believe that this cut-off point can be used in addition to laboratory data as a criterion for hospitalization, or patient treatment can be guided based on laboratory findings in cases where CT cannot be performed.

Authorship Contributions

Concept: O.G., C.O., S.U.R., Design: O.G., C.O., S.U.R., Data Collection or Processing: O.G., Z.N.S., A.B.Y., Analysis or Interpretation: O.G., S.U.R., S.K.C., Literature Search: O.G., C.O., S.U.R., Writing: O.G., S.U.R.

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Original Article

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Association Between COVID-19 and ABO Blood Groups: An Analysis on Convalescent Plasma Donors in Turkey

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Abstract

Aim: To investigate if there is an association between the blood groups of convalescent plasma (CP) donors and Severe acute respiratory syndrome Coronavirus-2 infection risk.

Methods: Blood groups of 30605 CP donors were compared with 1316676 Turkish Red Crescent (TRC) whole blood donors. Software data of TRC for the period between 07 April 2020 and 11 December 2020 was analyzed as a retrospective cohort study.

Results: Coronavirus disease-2019 (COVID-19) infection risks were higher in A (46.1% vs. 41.6%, p=0.001), AB (8.3% vs. 7.6%, p=0.001), Rh (+) (89.2% vs. 87.5%, p=0.001), A Rh (+) (41.1% vs. 36.6%, p=0.001) and AB Rh (+) (7.4% vs. 6.6%, p=0.001) groups; they were lower in O (29.8% vs. 34.4%, p=0.001), B (15.9% vs. 16.4%, p=0.008), Rh (-) (10.8% vs. 12.5%, p=0.001), B Rh (-) (1.7% vs. 2.0%, p=0.001), O Rh (+) (26.6% vs. 29.9%, p=0.001) and O Rh (-) (3.2% vs. 4.5%, p=0.001) groups.

Conclusions: There might be an increased COVID-19 risk in A, AB, Rh (+) and A Rh (+) and AB Rh (+) groups as well as a decreased risk in O, B, Rh (-) and O Rh (+), O Rh (-) and B Rh (-) groups.

Keywords: Convalescent plasma donors, blood groups, COVID-19, SARS-CoV-2, age, gender

Introduction

Coronavirus disease-2019 (COVID-19), which was reported to have emerged in Wuhan city of Hubei province of People's Republic of China with the etiologic agent Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) during last days of 2019, spread rapidly and led to a pandemic. At the time of this study, the virus has infected over 150 million people and led to the death over 3 million people in 224 countries/regions around the world (1). In Turkey, the number of cases reached around 5 million and about 41000 deaths occurred (2).

There is no definite cure for the disease yet. After the approval by U.S. Food and Drug Administration for emergency use of COVID-19 convalescent plasma (CP) for patients (3), Republic of Turkey Ministry of Health decided that COVID-19 CP could be used for the treatment of COVID-19 patients. In this context, Turkish Red Crescent (TRC) started accepting COVID-19 CP donations.

A relationship between the risk of developing SARS (also known as SARS caused by SARS-CoV-1 infection) with ABO blood type and the severity of associated complications was reported (4). The recent evidence has shown that there is also a relationship between ABO and Rh blood group systems and COVID-19 disease (5). The interest in the subject has started to increase after the publication of the study by Zhao et al. (6) which has shown for the first time that there is a higher risk of SARS-CoV-2 infection and COVID-19 disease for people with blood group A and a lower risk for people with blood group O.

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Different results in terms of the relationship between ABO and Rh groups and COVID-19 disease were revealed in two studies by Goker et al. (7) and Arac et al. (8) in Turkey. We compared the ABO blood group distribution of CP donors of TRC, who had been infected with and recovered from COVID-19 disease, with the healthy, voluntary and, non-remunerated donation blood donors of TRC; in order to analyze the relationship between ABO blood group system and contracting SARS-CoV-2 infection, using a larger sample group. Our aim is to investigate whether there is a significant difference between blood groups and the risk of contracting COVID-19.

Methods

Study Design

This study was approved by the Turkish Red Crescent Blood Services General Directorate Ethical Board (2021/4; 12.02.2021). Software data of TRC for the period between 07 April 2020 and 11 December 2020 was analyzed as a retrospective cohort study. In this period, a total of 30605 people have donated CP in TRC Blood Donation Centers. All these people were included in the study. Likewise all the 1316676 healthy, voluntary and, non-remunerated whole blood (WB) donors of TRC Blood Donation Centers were included as the control group in the study. Both CP and WB donations are accepted independent of the actual need for each blood groups. All the donors had given their consent before donation.

WB donors should be eligible to donate blood in accordance with the National Blood Guide (9), published by the Republic of Turkey Ministry of Health. The requirements per the COVID-19 CP Supply and Clinical Use Guide (10) published by the Republic of Turkey Ministry of Health for CP donation is as follows:

1- General requirements for being a WB donor and;

2- Positive laboratory test (nasopharynx swab polymerase chain reaction (PCR) test or SARS-CoV-2 antibodies serological test) and;

3- Fourteen days after resolution of clinical symptoms (cough, fever, dyspnea, fatigue etc.) and two negative PCR test results from nasopharyngeal swab (one of them should be performed in the last 48 hours) or;

4- If 28 days have passed after resolution of clinical symptoms, negative PCR test results are not necessary.

The repetitive donations in both groups were taken out from the data and only one blood group for one donor was analyzed. Blood groupings were performed with the Gel Centrifugation method; through Grifols (Grifols-Erytra, Spain) device and Grifols (Grifols, Spain) kits.

Statistical Analysis

For statistical analyses, frequency analysis was performed in variable groups and percentages were evaluated. Chi-squared analysis was implemented while analyzing the relationships between the groups of nominal variables. Chi-squared analysis was performed after checking the expected values in cells of 2x2 tables. The risk was estimated by contrasting the ratio of incidence in the group with the risk factor to the group without it. The results were regarded as significant if it was $p<0.05$. Analyses were made using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The average age of CP donors was (mean ± SD) 36.1±0.19; while it was 36.7±0.06 for the WB donors in control group. Gender distribution of CP donors and WB donors was as follows; males/females (%) 94/6; 88/12, respectively. In CP donors, the percentage of males was higher than WB donors since TRC does not accept plasma donations of any kind from females who have had any pregnancy history including miscarriages or D/C, due to the risk of transfusion-related acute lung injury in the recipient.

ABO and Rh blood group distribution of WB and CP donors are as shown in Figures 1 and 2.

When two blood donation groups were compared, A, AB and Rh (+) groups were found to be more common in CP group than WB group (p=0.001). CP group had significantly lower O, B and Rh (-) group rates than the WB control group (p=0.001, p=0.008 and p=0.001; respectively) (Table 1).

We performed detailed analyses in order to see if the significant differences of risk in certain groups persisted between genders and age groups. In this context, CP and WB donors have been categorized as young adulthood (18 to 35 years), middle-aged (36 to 55 years), and older adulthood (56 years and older) in accordance with Petry's study (11).

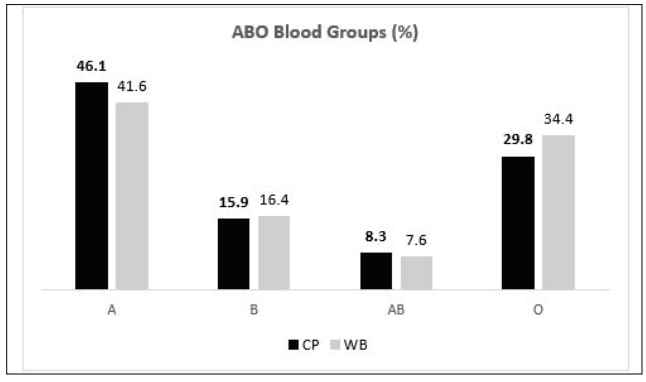

Figure 1. ABO blood group distribution among CP and WB donors
CP: Convalescent plasma WB: Whole blood

The significant risk difference observed in the A group between CP and WB donors has been observed in all male age groups and young adult females. The significant risk difference observed in the B group between CP and WB donors has not been observed in any gender and age groups. The significant risk difference observed in the AB group between CP and WB donors has been observed in young and middle-aged adult males and older adult females. The significant risk difference observed in the O group between CP and WB donors has been observed only in males of all age groups. The significant risk difference between Rh (+) and Rh (-) groups between CP and WB donors has been observed in young and middle-aged adult males and young adult females (Table 2).

A Rh (+) and AB Rh (+) groups were significantly higher in CP group, while B Rh (-), O Rh (+) and O Rh (-) group rates were found to be significantly lower (p=0.001) (Table 3).

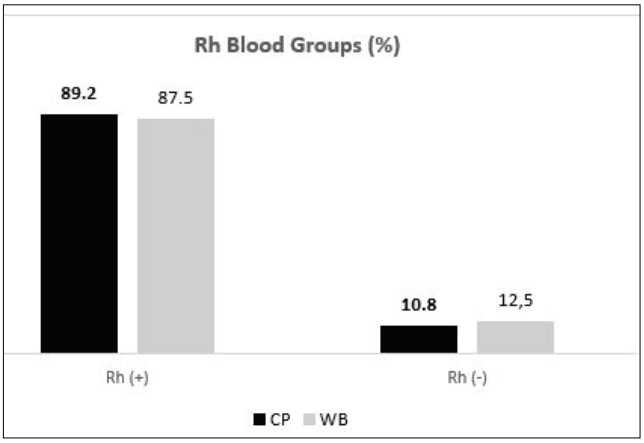

Figure 2. Rh blood group distribution among CP and WB donors
CP: Convalescent plasma, WB: Whole blood

Table 1. ABO and Rh blood group distribution in CP and WB donors

	CP n (%)	WB n (%)	p[a]	OR (95% CI)
A	14098 (46.1%)	548296 (41.6%)	**0.001**	1.20 (1.17-1.22)
B	4853 (15.9%)	216204 (16.4%)	**0.008**	0.96 (0.93-0.99)
AB	2541 (8.3%)	99423 (7.6%)	**0.001**	1.11 (1.06-1.16)
O	9113 (29.8%)	452753 (34.4%)	**0.001**	0.81 (0.79-0.83)
Rh (+)	27292 (89.2%)	1151592 (87.5%)	**0.001**	1.18 (1.14-1.23)
Rh (-)	3313 (10.8%)	165084 (12.5%)	**0.001**	0.85 (0.82-0.88)

[a]: Chi-square (x^2) test was used. There is a significant difference between all ABO blood groups in CP donors and WB donors. The reference for each group is all other 3 groups for ABO blood groups. The reference for the Rh group is the other Rh group. CP: Convalescent plasma, WB: Whole blood, OR: Odds ratio, CI: Confidence interval

Regarding the significant risk differences in different combinations of ABO and Rh groups, we performed detailed analyses to see if these persisted between genders and age groups.

The significant risk difference observed in the A Rh (+) group between CP and WB donors has been observed in males of all age groups and young adult females. The significant risk difference observed in the B Rh (-) group between CP and WB donors in young and middle-aged adult males and young adult females. The significant risk difference observed in the AB Rh (+) group between CP and WB donors in young and middle-aged adult males and older adult females. The significant risk difference observed in the O Rh (+) group between CP and WB donors only in males all of age groups. The significant risk difference observed in the O Rh (-) group between CP and WB donors has been observed in young and middle-aged adult males and middle-aged adult females (Table 4).

Discussion

In our study, we evaluated the risk association of COVID-19 infection with ABO and Rh blood groups in CP donors. There was a significantly increased risk in A, AB and Rh (+) groups in CP donors compared to the WB donors control group while a significantly decreased risk was observed in O, B and Rh (-) groups. A Rh (+) and AB Rh (+) groups had an increased risk while B Rh (-), O Rh (+) and O Rh (-) groups had a decreased risk for COVID-19 infection.

ABO antigens expressed on tissues such as epithelium and vascular endothelial cells as well as erythrocytes in humans were associated with various diseases (12). Rh (D) phenotypes were also associated with several diseases (13-15).

Zhao et al. (6) have shown for the first time that there is a higher risk of SARS-CoV-2 infection and COVID-19 disease for people with blood group A and a lower risk for people with blood group O. Although studies (7,16-24) and meta-analyses (25-27) from different continents and ethnicities verifying this relationship were published; studies which don't verify this relationship were also published (8,28-33). Goel et al. (34) attributed these different findings to different study populations, control groups, and geographical locations in addition to confounding factors such as age, comorbidities.

The higher risk of SARS-CoV-2 infection for blood group A versus blood group O is hypothetically attributed to the presence of anti-A antibodies in the serum of people with O blood group which can inhibit the virus-cell adhesion process by Khalil et al. (32). This might also explain the decreased risk in O and B blood groups in our study.

On the other hand, in our study, we detected that the risk of COVID-19 infection is increased in people with

Table 2. ABO and Rh blood group distribution in CP and WB donors by gender and age

		Male			Female		
	Age	**18-35**	**36-55**	**>55**	**18-35**	**36-55**	**>55**
A	**CP n (%)**	5702 (45.6%)	7141 (46.9%)	496 (44.4%)	694 (43.9%)	64 (40.5%)	1 (20.0%)
	WB n (%)	216608 (41.8%)	224481 (41.9%)	42229 (41.2%)	36933 (40.7%)	23762 (40.7%)	4283 (39.5%)
	p[a]	**0.001**	**0.001**	**0.031**	**0.011**	**0.97**	**0.373**
	OR (95% CI)[b]	1.17 (1.12-1.21)	1.23 (1.19-1.27)	1.14 (1.01-1.28)	1.14 (1.03-1.26)	0.99 (0.72-1.37)	0.38 (0.04-3.43)
B	**CP n (%)**	1988 (15.9%)	2427 (15.9%)	178 (15.9%)	240 (15.2%)	20 (12.7%)	0 (0%)
	WB n (%)	85645 (16.5%)	87050 (16.3%)	16912 (16.5%)	14909 (16.4%)	9819 (16.8%)	1869 (17.2%)
	p[a]	0.056	0.311	0.61	0.183	0.164	0.308
	OR (95% CI)[b]	0.95 (0.91-1.00)	0.98 (0.94-1.02)	0.96 (0.82-1.13)	0.91 (0.79-1.05)	0.72 (0.45-1.15)	-
AB	**CP n (%)**	1051 (8.4%)	1258 (8.3%)	94 (8.4%)	125 (7.9%)	11 (7.0%)	2 (40.0%)
	WB n (%)	39341 (7.6%)	40201 (7.5%)	7573 (7.4%)	6963 (7.7%)	4503 (7.7%)	842 (7.8%)
	p[a]	**0.001**	**0.001**	0.193	0.731	0.727	**0.007**
	OR (95% CI)[b]	1.12 (1.05-1.19)	1.11 (1.05-1.18)	1.15 (0.93-1.42)	1.03 (0.86-1.24)	0.89 (0.49-1.66)	7.92 (1.32-47.46)
O	**CP n (%)**	3777 (30.2%)	4398 (28.9%)	350 (31.3%)	523 (33.1%)	63 (39.9%)	2 (40.0%)
	WB n (%)	176727 (34.1%)	183991 (34.3%)	35842 (35.0%)	31980 (35.2%)	20364 (34.8%)	3850 (35.5%)
	p[a]	**0.001**	**0.001**	**0.011**	0.074	0.185	0.834
	OR (95% CI)[b]	0.84 (0.80-0.87)	0.78 (0.75-0.81)	0.85 (0.75-0.96)	0.91 (0.82-1.01)	1.24 (0.90-1.71)	1.21 (0.20-7.25)
Rh +	**CP n (%)**	11148 (89.1)	13599 (89.3)	991 (88.6)	1417 (89.6)	132 (83.5)	5 (100.0)
	WB n (%)	453919 (87.6%)	468901 (87.5%)	89957 (87.7%)	78756 (86.8%)	50570 (86.5%)	9489 (87.5%)
	p[a]	**0.001**	**0.001**	0.348	**0.001**	0.274	0.398
	OR (95% CI)[b]	1.16 (1.09-1.22)	1.19 (1.13-1.26)	1.09 (0.91-1.32)	1.31 (1.12-1.54)	0.79 (0.52-1.21)	-
Rh -	**CP n (%)**	1370 (10.9%)	1625 (10.7%)	127 (11.4%)	165 (10.4%)	26 (16.5%)	0 (0%)
	WB n (%)	64402 (12.4%)	66822 (12.5%)	12599 (12.3%)	12029 (13.3%)	7878 (13.5%)	1355 (12.5%)
	p[a]	**0.001**	**0.001**	0.348	**0.001**	0.274	0.398
	OR (95% CI)[b]	0.87 (0.82-0.92)	0.84 (0.80-0.88)	0.92 (0.76-1.10)	0.76 (0.65-0.90)	1.26 (0.83-1.93)	-

[a]: Chi-square (x^2) test was used. There is a significant difference between all ABO blood groups in CP donors and WB donors. There is a significant difference between Rh blood groups in CP donors and WB donors.
[b]: The analyses were performed for each gender and age groups separately and the risks for ABO blood groups show the risk in reference to all other ABO blood groups for this gender and age group. Likewise, the risks for Rh blood groups show the risk in reference to the other Rh blood group for this gender and age group. CP: Convalescent plasma, WB: Whole blood, OR: Odds ratio, CI: Confidence interval

Table 3. ABO-Rh type blood group distribution in CP and WB donors

	CP n (%)	**WB n (%)**	**p[a]**	**OR (95% CI)**
A Rh (+)	12579 (41.1%)	482390 (36.6%)	**0.001**	1.21 (1.18-1.24)
A Rh (-)	1519 (4.9%)	65906 (5.0%)	0.738	0.99 (0.94-1.04)
B Rh (+)	4332 (14.2%)	189655 (14.4%)	0.219	0.98 (0.95-1.01)
B Rh (-)	521 (1.7%)	26549 (2.0%)	**0.001**	0.84 (0.77-0.92)
AB Rh (+)	2255 (7.4%)	86506 (6.6%)	**0.001**	1.13 (1.08-1.18)
AB Rh (-)	286 (0.9%)	12917 (1.0%)	0.414	0.95 (0.85-1.07)
0 Rh (+)	8126 (26.6%)	393041 (29.9%)	**0.001**	0.85 (0.83-0.87)
0 Rh (-)	987 (3.2%)	59712 (4.5%)	**0.001**	0.70 (0.66-0.75)

[a]: Chi-square (x^2) test was used. There is a significant difference between all ABO and Rh blood groups in CP donors and WB donors. The reference for each group is all other groups. CP: Convalescent plasma, WB: Whole blood, OR: Odds ratio, CI: Confidence interval

Rh (+) while it is decreased in people with Rh (-). Several studies revealed that people with Rh (+) have an increased risk of COVID-19 infection (8,30,35) while people with Rh (-) has decreased risk (8,36). Contrary to our study and the literature in general, one study has suggested that Rh (+) blood types are less susceptible to COVID-19 (33). Another study has found no significant difference regarding Rh blood groups (29).

Table 4. ABO-Rh type blood group distribution in CP and WB donors by gender and age

		Male			Female		
	Age	**18-35**	**36-55**	**>55**	**18-35**	**36-55**	**>55**
A Rh +	**CP n (%)**	5082 (40.6%)	6380 (41.9%)	444 (39.7%)	619 (39.1%)	53 (33.5%)	1 (20.0%)
	WB n (%)	190925 (36.8%)	197388 (36.9%)	37181 (36.3%)	32305 (35.6%)	20808 (35.6%)	3783 (34.9%)
	p[a]	**0.001**	**0.001**	**0.017**	**0.004**	0.59	0.485
	OR (95% CI)[b]	1.17 (1.13-1.215)	1.24 (1.20-1.28)	1.16 (1.03-1.31)	1.16 (1.05-1.29)	0.91 (0.66-1.27)	0.47 (0.05-4.18)
A Rh -	**CP n (%)**	620 (5.0%)	761 (5.0%)	52 (4.7%)	75 (4.7%)	11 (7.0%)	0 (0%)
	WB n (%)	25683 (5.0%)	27093 (5.1%)	5048 (4.9%)	4628 (5.1%)	2954 (5.1%)	500 (4.6%)
	p[a]	0.991	0.745	0.677	0.522	0.274	0.623
	OR (95% CI)[b]	1.01 (0.92-1.09)	0.99 (0.92-1.06)	0.94 (0.71-1.25)	0.93 (0.73-1.17)	1.41 (0.76-2.60)	-
B Rh +	**CP n (%)**	1779 (14.2%)	2160 (14.2%)	157 (14.0%)	221 (14.0%)	15 (9.5%)	0 (0%)
	WB n (%)	75217 (14.5%)	76445 (14.3%)	14909 (14.5%)	12981 (14.3%)	8464 (14.5%)	1639 (15.1%)
	p[a]	0.346	0.777	0.641	0.711	0.075	0.345
	OR (95% CI)[b]	0.98 (0.93-1.03)	0.99 (0.95-1.04)	0.96 (0.81-1.14)	0.97 (0.84-1.12)	0.62 (0.36-1.06)	-
B Rh -	**CP n (%)**	209 (1.7%)	267 (1.8%)	21 (1.9%)	19 (1.2%)	5 (3.2%)	0 (0%)
	WB n (%)	10428 (2.0%)	10605 (2.0%)	2003 (2.0%)	1928 (2.1%)	1355 (2.3%)	230 (2.1%)
	p[a]	**0.007**	**0.048**	0.857	**0.011**	0.48	0.742
	OR (95% CI)[b]	0.827 (0.72-0.95)	0.88 (0.78-1.00)	0.96 (0.62-1.48)	0.56 (0.36-0.88)	1.38 (0.56-3.36)	-
AB Rh +	**CP n (%)**	936 (7.5%)	1115 (7.3%)	82 (7.3%)	109 (6.9%)	11 (7.0%)	2 (40.0%)
	WB n (%)	34318 (6.6%)	34938 (6.5%)	6629 (6.5%)	6013 (6.6%)	3888 (6.7%)	720 (6.6%)
	p[a]	**0.001**	**0.001**	0.239	0.673	0.876	**0.003**
	OR (95% CI)[b]	1.14 (1.07-1.22)	1.13 (1.07-1.21)	1.15 (0.91-1.44)	1.04 (0.86-1.27)	1.05 (0.57-1.94)	9.37 (1.56-56.19)
AB Rh -	**CP n (%)**	115 (0.9%)	143 (0.9%)	12 (1.1%)	16 (1.0%)	0 (0%)	0 (0%)
	WB n (%)	5023 (1.0%)	5263 (1.0%)	944 (0.9%)	950 (1.1%)	615 (1.1%)	122 (1.1%)
	p[a]	0.569	0.595	0.595	0.892	0.195	0.811
	OR (95% CI)[b]	0.94 (0.79-1.14)	0.96 (0.81-1.13)	1.17 (0.66-2.07)	0.97 (0.59-1.59)	0.99 (0.99-0.99)	-
O Rh +	**CP n (%)**	3351 (26.8%)	3944 (25.9%)	308 (27.6%)	468 (29.6%)	53 (33.5%)	2 (40.0%)
	WB n (%)	153459 (29.6%)	160130 (29.9%)	31238 (30.5%)	27457 (30.2%)	17410 (29.8%)	3347 (30.9%)
	p[a]	**0.001**	**0.001**	**0.035**	0.57	0.302	0.658
	OR (95% CI)[b]	0.87 (0.84-0.91)	0.82 (0.79-0.85)	0.87 (0.76-0.99)	0.97 (0.87-1.08)	1.19 (0.86-1.66)	1.49 (0.25-8.94)
O Rh -	**CP n (%)**	426 (3.4%)	454 (3.0%)	42 (3.8%)	55 (3.5%)	10 (6.3%)	0 (0%)
	WB n (%)	23268 (4.5%)	23861 (4.5%)	4604 (4.5%)	4523 (5.0%)	2954 (5.1%)	503 (4.6%)
	p[a]	**0.001**	**0.001**	0.239	**0.006**	0.465	0.622
	OR (95% CI)[b]	0.75 (0.68-0.83)	0.66 (0.60-0.73)	0.83 (0.61-1.13)	0.69 (0.52-0.90)	1.27 (0.67-2.41)	-

[a]: Chi-square (x^2) test was used. There is a significant difference between all ABO and Rh blood groups in CP donors and WB donors. The reference for each group is all other groups for ABOand Rh blood groups.
[b]: The analyses were performed for each gender and age groups separately and the risks for ABO and Rh blood groups show the risk in reference to all other ABOand Rh blood groups for this gender and age group. CP: Convalescent plasma, WB: Whole blood, OR: Odds ratio, CI: Confidence interval

In our study, we detected an increased risk in A Rh (+) blood group with a decreased risk in the O Rh (+) blood group. Taha et al. (19) found similar results. Different from the literature, there was an increased risk in AB Rh (+) group while there were decreased risks in B Rh (-), O Rh (+) and O Rh (-) groups in our study. While a decreased risk was found in group B and increased risk in Rh (+), the combination, B Rh (+), did not have either an increased or a decreased risk. The same also applied to the combinations A Rh (-) and AB Rh (-). These results implicated that the virus has a tendency to infect individuals with Rh antigen. There was a decreased risk in group O regardless of Rh groups, possibly due to the presence of anti-A antibodies.

Different from the literature, an increased risk in the AB group was found in our study similar to the results of only 4 studies (29,30,33,37). Zhao et al. (6) also reported an increased risk in the AB group in one of three different hospitals in their study. However, a decreased risk was observed in B group in our study while an increased risk was found in the B groups in 3 studies (30,33,37).

The significant differences we found between CP and WB donors for different gender and age groups were not persistent through all genders and age groups. We have searched the relevant literature using the keywords; "convalescent plasma donors", "blood groups", "COVID-19", "SARS-CoV-2", "age", "gender". However, we have not identified any studies in which the risk of COVID-19 distribution in ABO and Rh group combinations by gender and age were studied.

Regarding the relationship between ABO blood group types and COVID-19 and the underlying molecular mechanisms, some hypotheses have been suggested (34,38). Gérard et al. (39) suggested the hypothesis that O group patients have a decreased risk compared to all other groups, while people with both O and B blood groups have anti-A antibody in the plasma; and hence, anti-A antibody of O group is more protective than the anti-A antibody of B group. This hypothesis may support the findings of our study such that the strong protective anti-A antibody in O group in our study was not affected by the Rh factor and the weaker protective anti-A antibody in B group was affected by Rh factor, in terms of COVID-19 risk.

Focosi (40) also stated in his research that anti-B antibody, mainly with anti-A antibody, can also be protective against COVID-19. In fact, based on this hypothesis, he suggested to prefer using the CP of O group donors in order to be more effective in treatment. This hypothesis might explain the decreased risk in O and B groups and the increased risk in the AB group in our study. On the other hand, Kotila et al. (37) expressed that the decreased risk in blood group O could be due to potent anti-B antibodies; however, this explanation does not support our finding of an increased risk in blood group A.

Another hypothesis by Zaidi et al. (41) stated that blood groups were determined by sugars such as N-acetyl galactosamine, and coronaviruses in human have surface proteins that bind to these sugars. N-acetyl galactosamine, the extra sugar on the surface of A blood group cells, could possibly be important for more pathogen exposure. This sugar is deficient in O blood group cells. This hypothesis might support the increased risk in the A group and decreased risk in the O group in our study.

Study Limitations

One limitation of our study is that we were not able to evaluate other potential risk factors such as smoking since this is a retrospective study. For WB/CP donation we do not inquire smoking status. However, we would expect both CP and WB donors to be in similar medical status because CP donors should basically meet the same medical requirements as the WB donors. By definition, CP donors are a subset of WB donors who had COVID-19 infection and then recovered. Severe medical conditions such as chronic kidney failure, chronic heart failure, active malignancy or malignancy history, ischemic heart disease, severe chronic obstructive lung disease, insulin-dependent Diabetes Mellitus require permanent deferral for WB/CP donors.

Another limitation of our study is that the study population is composed of WB/CP donors; which might decrease the representation of the country population. However, all of the patients who recovered from COVID-19 were invited by TRC for CP donation, the blood donors were from the different cities of the country with the advantage of TRC, being the responsible body for donation; and the large study and comparison group numbers increase the power of the study.

Conclusion

The first question is "Are blood groups independent risk factors for the development of COVID-19?". While there was an increased risk of infection in A, AB and Rh (+) groups, there was a decreased risk in O, B and Rh (-) groups in our study. Again, there was an increased risk in A Rh (+) and AB Rh (+) and decreased risk in B Rh (-), O Rh (+) and O Rh (-). The second question is the decreased risk in group O related to high concentrations of circulating anti-A and anti-B antibodies of these people? Could Rh antigen be a cause of affinity for the virus and increase the risk? It appears that there is a need for further research into the underlying mechanisms.

Authorship Contributions

Concept: M.Y., A.K., N.N.S., M.N.G., N.H., K.K., F.M.Y., Design: M.Y., A.K., N.N.S., M.N.G., N.H., K.K., F.M.Y., Data Collection or Processing: N.N.S., G.G.K., Analysis or Interpretation: N.N.S., G.G.K., Literature Search: A.K., Writing: M.Y., A.K.

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Effect of COVID-19 Pandemic on the Working of Blood Transfusion Center: A Cross-Sectional Study

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Abstract

Aim: Coronavirus disease-2019 (COVID-19) disease which is unknown how much it will affect the work of hospitals, has caused a pandemic all over world. The decrease in donations due to pandemic required regulation of blood supply in hospitals. In our study, we aimed to evaluate the blood center of our hospital during the pandemic period.

Methods: Patients' records of our hospital blood transfusion center were reviewed retrospectively before and during the pandemic. The patients were divided into two groups as pre-pandemic (11 March-30 June 2019) and pandemic period (11 March-30 June 2020). The groups were compared in terms of age range, gender, blood type, blood type of products, diseases causing transfusion, blood/blood products transfusion/counts, transfusions performed to COVID-19 patients.

Results: Four thousand two hundred seventy-one blood product transfusions were performed on 1,290 patients. Evaluation of diseases that cause transfusion among statistically significant groups in some diseases such as gastrointestinal diseases, genitourinary system diseases, infectious diseases and other diseases was determined.

Conclusion: While a decrease in our transfusion rates was observed during the pandemic period, the increase in gastrointestinal system diseases is a striking result. The modern world will encounter these and similar pandemics in the future and we think that each region should evaluate its own blood centers in order to prepare for them.

Keywords: Blood cells, blood transfusion, pandemics, transfusıon medicine

Introduction

An outbreak of pneumonia of unknown cause occurred in Wuhan, China, in December 2019. As a result of the investigations, a new coronavirus, Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) was detected as the cause of this new pneumonia, and this disease was named as Coronavirus disease-2019 (COVID-19) disease (1). It resulted in a pandemic that spread rapidly all over the world. In many viral diseases, both blood donation and blood transfusion procedures can't be applied due to the incubation period, disease-related fever, etc. (2).

The spread of COVID-19 has had a serious impact on blood donation numbers, blood supply and blood safety. The incubation period of SARS-CoV-2 is usually 1-14 days; while the average is 5-6 days, the longest reported is 24 days (3). China, which is considered the starting point of the pandemic, became the first country with a problem in blood transfusion and regulations were made in the country for blood donation (4). Blood center records should be reviewed and blood and blood product sources should be managed as efficiently as possible. The demand must be fully evaluated and a system must be formulated for the emergency supply, demand and use of the blood supply.

With this information, we thought that we should examine the use of blood products in our own hospital. Therefore, our study not only reflects the state of our blood center, but can also guide scientists on what kind of supply and demand might be in other global pandemics. Based on this idea, we aimed to evaluate the blood center

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of our hospital and analyze how it was affected by the pandemic process.

Methods

Study Design

The study was conducted in accordance with the Declaration of Helsinki; Ethics committee approval was obtained from the local Kastamonu Training and Research Hospital Clinical Research Ethics Committee (date: 21/12/2020 and approval number: 2020-KAEK-143-11.01). The personal information of the patients was not used, only the data obtained from the blood center records were evaluated. Therefore, permission was obtained from the hospital manager for the examination of records, and there was no need to obtain individual patient consent.

Data Collection

The present cross-sectional study includes the data of the Blood Transfusion Center of the Kastamonu Traning and Research Hospital and blood and blood product transfusions performed between the pre-pandemic period (11 March-30 June 2019) and the pandemic period (11 March-30 June 2020) were determined. In the study, two different periods were compared, namely the pre-pandemic period and the pandemic period. For this purpose, data on a total of 1,290 patients, including 747 patients followed up during the pandemic period and 543 patients followed in the pre-pandemic period, were used. Transfusions consist of 4,271 blood product transfusions, including 3234 erythrocytes suspensions (ES), 725 fresh frozen plasma (FFP) and 312 platelet suspensions (TS).

Data Assessment

The age range, gender, blood type of the patient, the blood type of the transfused product, the diseases that caused the patient's transfusion, and the amount of transfusion performed in the blood center during or before the pandemic were examined. Transfusions for COVID-19 patients have been determined. These patients in the infectious diseases group were taken as COVID-19 definite or doubtful. Patients with a definite diagnosis have positive COVID-19 polymerase chain reaction (PCR) performed by our hospital's laboratory. While the COVID-19 PCR test was negative, there were patients considered suspicious according to lung tomography imaging, and the transfusions applied to these patients were evaluated as transfusions to patients suspected of COVID-19 disease.

Statistical Analysis

Data obtained from blood center records were encoded and analyzed using SPSS version 22 (IBM). Descriptive analysis was performed to calculate frequencies and ratios. Chi-square test, Kruskal-Wallis test, Fisher's Exact test were used to examine the level of the relationship between variables. The $p<0.005$ was considered statistically significant.

Results

Four thousand two hundred seventy-one blood and blood product transfusions were performed on a total of 1,290 patients, including 747 patients treated in the pre-pandemic period and 543 patients followed up during the pandemic period. It was observed that 37 transfusions were made in 17 patients who were positive for COVID-19 during the pandemic period. This consists of 28 ES transfusions for 13 patients, 7 FFPs for 3 patients and 2 TS transfusions for 1 patient. When examining the distribution of the patients in terms of age, gender and blood groups in demographic evaluations; there was a difference in terms of gender (p=0.034) (Table 1).

When the groups of blood and blood products used in the patients were evaluated, there was no difference in shoes (p=0.087) between the periods (Graphic 1).

When the use of ES (p=0.104), FFP (p=0.307) and TS (p=0.232) between the periods of the followed-up patients was examined; it was determined that there was no statistically significant difference between the periods for all three (Graphic 2).

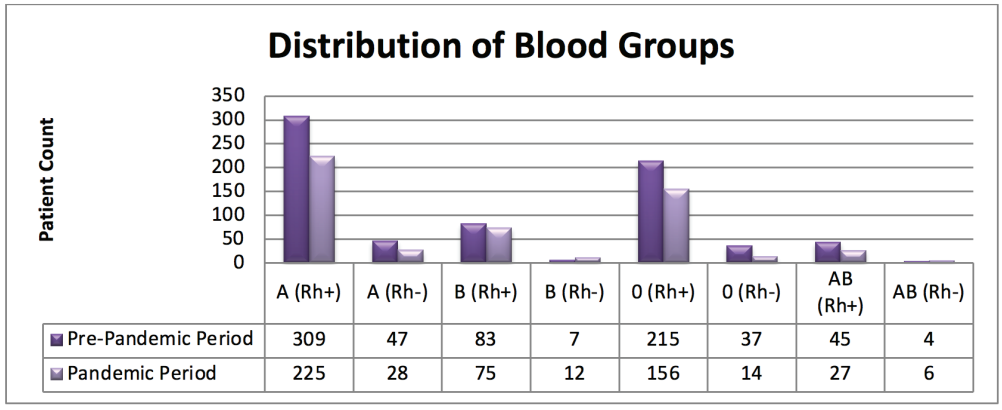
While the ratio of female patients, which was 60.8% in the pre-pandemic period, to 54.9% during the pandemic period, the rate of male patients increased from 39.2% to 45.1%.

When the distribution of blood groups is examined, the majority of patients for both periods A Rh (+) (41.4% for both periods) and 0 Rh (+) (28.8% for the pre-pandemic period and 28.7% for the pandemic period) blood groups and distributions to other blood groups are also similar.

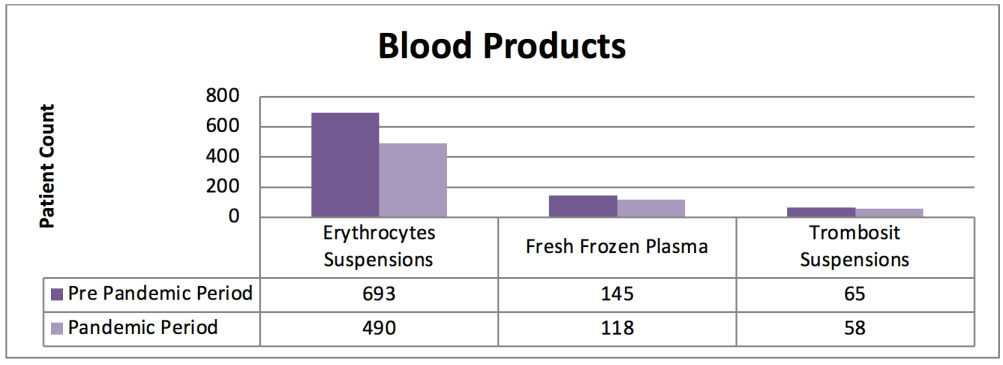
When the diseases that cause transfusion were compared between periods, there was no statistically significant difference between the two periods in terms of however transfusion due to the musculoskeletal system diseases and trauma (p=0.03) the presence of endocrine, nervous system diseases, cardiovascular system diseases and respiratory diseases (p>0.05). bleeding-phytic system

Table 1. Age, gender, blood type of transfusions and classification of products used between periods

Factor	Group	Period		p
		Pre pandemic	Pandemic	
Age range	18-30	145 (19.4%)	118 (21.7%)	0.137
	31-50	65 (8.7%)	58 (10.7%)	
	51-70	209 (28.0%)	134 (24.7%)	
	>70	421 (56.4%)	336 (61.9%)	
Gender	Female	454 (60.8%)	298 (54.9%)	0.034
	Male	293 (39.2%)	245 (45.1%)	
There was a difference in terms of gender (p=0.034) (chi-square test)				



Graphics 1. Distribution of blood groups



Graphic 2. Distribution of used blood products to patients

It was determined that there is a difference (p<0.05) in terms of diseases, gastrointestinal diseases (p=0.03), genitourinary system diseases (p<0.01), infectious diseases (p<0.01) and other diseases (malignancy, hematology, etc.) (p<0.01) (Table 2).

When the use cases of ES, FFP and TS were examined according to the COVID-19 conditions of 543 patients treated during the pandemic period, there was no statistically significant difference between the groups for ES and FFP (p>0.05), while for TS there was a significant difference (p<0.05) has been determined. The rate of patients using TS is 8.9% in the Negative group, 25.5% in the Suspect group and 4.3% in the Positive group (Table 3).

When the amount of ES, FFP and TS usage in terms of COVID-19 groups of patients followed up during the pandemic period; It was determined that there was a statistically significant difference between the periods in terms of the amount of ES (p=0.046) use, and no difference for the amount of FFP (p=0.973) and TS (p=0.362) use. The mean of ES use of 430 patients using ES in the Negative group was 2.91±2.27, this average was calculated as 3.51±2.69 in the Suspect group and 2.15±2.12 in the Positive group. The mean use of FFP and TS was 2.35±1.85 and 2.10±1.43 in the Negative group, 2.21±1.37 and 2.64±2.41 in the suspect group, respectively and 2.33±1.53 and 1.00±0.0 in the positive group.

Table 2. Comparison of diseases that cause transfusion between periods

Diseases that cause transfusion	Period		p
	Pre-pandemic	Pandemic	
Endocrine diseases	13 (1.7%)	6 (1.1%)	0.350
Nervous system diseases	85 (11.4%)	50 (9.2%)	0.209
Musculoskeletal system and trauma	147 (19.7%)	73 (13.4%)	0.003
Cardiovascular diseases	70 (9.4%)	55 (10.1%)	0.650
Gastrointestinal system diseases	111 (14.9%)	115(21.2%)	0.003
Respiratory diseases	111 (14.9%)	71 (13.1%)	0.364
Genitourinary system diseases	141 (18.9%)	55 (10.1%)	<0.001
Contagious disease presence or suspected	1 (0.1%)	67 (12.3%)	<0.001
Other (malignancy, hematology etc.)	298 (39.9%)	165 (30.4%)	<0.001

Musculoskeletal diseases (p=0.03), gastrointestinal diseases (p=0.03), genitourinary system diseases (p<0.01). infectious diseases (p<0.01) and other diseases (malignancy, hematology. etc.) (p<0.01) due to a statistically significant difference was observed between the periods in transfusions, (chi-square test)

Table 3. ES, FFP and TS usage status of patients according to COVID-19 status during pandemic

	COVID-19	n	Mean±SD	p
ES	Negative	430	2.91±2.27	0.046*
	Suspect	47	3.51±2.69	
	Positive	13	2.15±2.12	
FFP	Negative	101	2.35±1.85	0.973
	Suspect	14	2.21±1.37	
	Positive	3	2.33±1.53	
TS	Negative	42	2.10±1.43	0.362
	Suspect	14	2.64±2.41	
	Positive	2	1.00±0.00	

When the COVID-19 groups of the patients followed up during the pandemic period were examined in terms of the amount of ES use, it was found that there was a statistically significant difference (p=0.046) between the periods (Kruskal-Wallis test). TS was examined according to the COVID-19 conditions of the patients treated during the pandemic period, there was a significant difference (p=0.01) has been determined (Fisher's Exact test). ES: Erythrocytes suspensions, TS: Trombosit suspensions, FFP: Fresh frozen plasma, COVID-19: Coronavirus disease-2019

Discussion

In our study, a decrease of 27.3% was observed in the transfusions applied during the pandemic period compared to the pre-pandemic period. Al-Riyami et al. (5), evaluated the blood centers of 16 countries in the Eastern Mediterranean Region, 75% of whom were national blood relatives and observed a decrease in their demand in most centers. Our study is compatible with the literature in this respect. In general, while the number of transfusions decreased during the pandemic period, it was observed that there was a relative increase in the need for transfusion in male patients as an interesting result of our study.

In the study of Barriteau et al. (6), 41 (13.4%) of 305 COVID-19 patients hospitalized were transfused, of which: 33 (11.1%) red blood cells (RBC), 5 (1.6%) platelets (PLTs) reported that 3 (1.0%) plasma transfusions were performed. In our study, we found that ES transfusion was used the most in COVID-19 patients, and then FFP and TS were used. The proportional distribution of our transfusions among blood products is consistent with this study.

A study examined the distribution of blood groups from community populations and patients with COVID-19 disease, and it was shown that blood group A was associated with an increased risk of infection, while blood type 0 was associated with low risk (7). Our study shows that the blood product that should be supplied the most before and during the pandemic period is the products belonging to the A Rh (+) blood group and it is compatible with the literature. As an interesting result in our study, it was determined that although there are products belonging to the A blood group, which we identify as the most common blood type and which we use the most in general transfusions, in COVID-19 patients, blood products belonging to the 0 blood group are mostly needed.

Another study examined the relationship of AB0 blood groups with COVID-19 disease and evaluated the relationship between the presence of IgG anti-a and this disease as a subgroup. As a result, analyzing the data in this way strongly indicates that the presence of anti-A antibodies, and more specifically IgG anti-A, in serum should be considered as a more important factor than the blood type itself, relative to the relationship with COVID-19. According to this result, there is a correlation between COVID-19 sensitivity and ABO blood types (8). In this context, transfusion process and blood/blood product supply are also very important.

During the COVID-19 pandemic, the selection and preparation of patients who require orthopedic surgery are important and a certain standard has been tried to be established in this regard. In our study, it is observed that the transfusion rates of those performed due to musculoskeletal system diseases during the pandemic period decreased (9). We are of the opinion that the reason for this lowness may be the limitations applied due to the pandemic, the reduction of elective surgeries and the reduction of traumas.

Xiao et al. (10) reported in their study that the SARS-CoV-2 virus infects epithelial cells of the stomach, duodenum and rectum. Gu J et al. (11), described COVID-19 disease, increased transaminases, hypoproteinemia, and liver damage caused by prolongation in prothrombin time in their study. In our study, it was observed that transfusions performed due to gastrointestinal diseases increased. The reason for this is that, when epithelitis occurring in the gastrointestinal system and accompanying bleeding disorders come together, it may cause microgastrointestinal hemorrhages in patients. Bleeding of stress ulcers caused by psychological problems during the pandemic period and the use of antiaggregant or anticoagulant drugs during this period may be another reason.

While transfusions originating from the genitourinary system, it regressed during the pandemic period. It was thought that the reason for this situation was the fact that more transfusions were used in elective operations and the number of transfusions naturally decreased when these operations were delayed.

Transfusions in infectious diseases have increased. Hematological changes that occur in COVID-19 disease have been reported to cause normal or slightly decreased hemoglobin and thrombocyte values in most patients (12,13). Here, of course, in most infectious diseases, bleeding disorder is not observed, but in COVID-19 disease, required regulation is affected. In our study, 60

patients with COVID-19 suspicious and positive patients were treated with ES, 17 patients with FFP and 16 patients with TS transfusion, and naturally, a statistically significant difference was observed between the periods.

Daily routine transfusions are procedures that cover blood losses due to surgery, trauma and oncological reasons. 15% of erythrocyte transfusions are reserved for hematology and oncology patients (14). In our study, transfusions performed for other reasons decreased during the pandemic period. It is thought that among the reasons for this, routine transfusion patients do not want to come to the hospital due to fear of getting sick, doctors make the decision of transfusion more difficult, reduction of elective surgeries, etc.

In studies conducted, immune plasma therapy appears to be safe, clinically effective in COVID-19 patients, and there are opinions that it reduces mortality (15,16). FFPs included in the study were used in the usual indications in bleeding diathesis, warfarin-related bleeding, prolonged INR, liver failure, as a protein and nutrient source (in albumin deficiency), vitamin K-dependent coagulation factor deficiency, massive transfusion protocol and DIC (17).

Although COVID-19 disease is a viral respiratory disease that can cause the severe acute respiratory syndrome, it may cause susceptibility to thrombotic disease in both venous and arterial circulation, platelet activation disorder, endothelial dysfunction and stasis due to excessive inflammation in patients (18). Chen et al. (19), investigated whether COVID-19 was associated with significant thrombocytopenia in their study, and thrombocytopenia was observed in 12% of their patients. Investigation of the etiology of thrombocytopenia, clinical history, laboratory values, complete blood count and peripheral smear examination are essential components of the diagnostic study, and physicians should be knowledgeable in the appropriate selection and interpretation of these specific tests. In our study, the rate of platelet use increased from 8.7% in the pre-pandemic period to 10.7% in the pandemic period. The difference is not statistically significant, but clinically, this increase, which is concurrent with COVID-19 disease, is significant. We do not yet know how much the COVID-19 pandemic will affect the operation of blood transfusion centers, but the literature should recommend to be prepared (20,21).

Study Limitations

The limitations of the study are that it is a single center study and the number of transfusions in COVID-19 patients is low because it was conducted at the beginning of the pandemic process. In future studies, evaluation of transfusions made only to COVID-19 patients can give more information to science about the use of blood and blood products in the pandemic. Despite these limitations, we showed in our study that there was a decrease in blood transfusions, an increase in transfusions performed for gastrointestinal reasons and that blood group 0 products were used more in our hospital during the pandemic period.

Conclusion

Clearly, the decrease in our transfusion rates can be traced in our data results. Another reason for the decrease in the number of transfusions may be that the decision of transfusion becomes more difficult for physicians. In these times when it is not known how long the pandemic will last, more extensive and multi-center studies are needed to use the blood center resources more efficiently. In our study, the increase in transfusion performed in infectious diseases can be considered as a natural result. However, the increase in gastrointestinal system diseases is a striking result. As an interesting result, we found that we mostly use blood products belonging to the 0 blood group in COVID-19 patients, although there are products belonging to the A blood group that we identify as the most common blood group and which we use the most in general transfusions. It is very likely that the modern world will encounter this and similar pandemics in the future periods. We think that each region should evaluate its own blood centers.

Authorship Contributions

Concept: A.Y., H.C.Z., B.A.., Z.E., Design: A.Y., H.C.Z., B.A.., Z.E., Data Collection or Processing: A.Y., H.C.Z., B.A.., Z.E., Analysis or Interpretation: A.Y., H.C.Z., B.A.., Z.E., Literature Search: A.Y., H.C.Z., B.A.., Z.E., Writing: A.Y., H.C.Z., B.A.., Z.E.

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Original Article

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Evaluation of Urine Polymerase Chain Reaction Test Positivity Rates and the Effectiveness of Positron Emission Tomography in Renal Involvement in Patients with Active COVID-19 Infection: A Prospective and Multidisciplinary Study

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Abstract

Aim: It is known that the Coronavirus disease-2019 (COVID-19) does not only affect the respiratory system in the body, but also affects many vital systems. In this study, we aimed to investigate polymerase chain reaction (PCR) positivity rates in urine samples of patients with COVID-19 infection and to evaluate the effectiveness of positron emission tomography/computed tomography (PET/CT) in demonstrating renal involvement in patients with urinary system involvement findings.

Methods: Patients who had positive COVID-19 PCR test and were hospitalized in Erciyes University pandemic wards due to COVID-19 infection between June 2020 and December 2020 were included in this prospective study. A urine PCR test was applied to all patients. In addition, PET/CT was performed in patients with no known malignancy, clean urine culture, but suspected COVID-19 urinary system involvement.

Results: A total of 66 patients with a mean age of 45.4±9.1 years were included in the study. PET/CT was performed at the same time in 6 of these patients with suspected urinary system involvement. Only 1 (1.5%) of 66 patients had a positive urine PCR test. No abnormal genitourinary PET/CT findings were found in any of the patients.

Conclusion: Urine PCR positivity is very rare in patients with COVID-19 infection. In addition, according to our results, it can be said that PET/CT is not an effective imaging method to show COVID-19 urinary system involvement.

Keywords: COVID-19, coronavirus, urine, PCR, PET/CT

Introduction

Infection factors have caused great morbidity and mortality at different periods in history. Ergotism in 11th century, smallpox in 12th century, leprosy in 13th century, syphilis in 15th century, dysentery in 16th century, tuberculosis in 17th century, typhoid in 18th century, cholera in 19th century, HIV/AIDS in 20th century, but at the beginning of the 21st century, "Severe acute respiratory syndrome (SARS)", caused which is a coronavirus, started to threaten the world (1). About 18 years after that epidemic, a new Coronavirus disease-2019 (COVID-19) outbreak in Wuhan

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spread rapidly to China and then became a global public health problem (2).

In previous reports, it has been reported that COVID-19 can affect not only the respiratory system but also other systems. One of these systems is the urogenital system, and although coronaviruses are basically isolated from the respiratory tract epithelium, it is a matter of curiosity and still controversial whether this virus can be isolated from other body fluids, especially urine (3,4).

Positron emission tomography/computed tomography (PET/CT) is an imaging method used in medicine and often in the diagnosis of oncological diseases. However, it is known that the imaging method used in PET/CT is an indicator not only in oncological conditions but also in infectious and inflammatory conditions (5-7). For this reason, it is important to investigate whether PET/CT, whose use is increasingly widespread with the developing technology, can show organ involvement in coronavirus, in terms of determining new diagnostic methods that can be used in this disease.

In this study, it was aimed to investigate both the isolation of coronavirus from urine and to evaluate the effectiveness of PET/CT in showing urinary organ involvement in COVID-19 patients whose kidneys were affected.

Methods

Patient Selection and Study Design

After the ethical approval Ethics Committee of Erciyes University, (approval number: 2020/198 and date: 06.04.2020), patients who were hospitalized in Erciyes University pandemic wards due to COVID-19 infection between June 2020 and December 2020 were included in this prospective study. COVID-19 polymerase chain reaction (PCR) was studied from urine samples of patients between the ages of 18-70 years, who had no active urinary tract infection, and who had a positive COVID-19 PCR test in the throat swab sample in the last 24 hours. The COVID-19 PCR test was positive in the throat swab sample taken within the last 72 hours and the kidney functions [serum creatinine and glomerular filtration rate (GFR)] were normal before, but the renal function deteriorated after COVID-19 (serum creatinine >2 mg/dL and/or patients with GFR <60 mL/min/1.73 m^2) underwent PET/CT. Those with known malignancies, those with previously impaired renal function, known urinary tract stone disease, demonstrated hydronephrosis, those with positive urine culture test, those with known infectious-inflammatory disease (autoimmune, rheumatic, etc.) other than COVID-19, PET/CT withdrawal contraindicated patients (pregnancy, etc.) were excluded from the study. Urine COVID-19 PCR test was also applied to these patients simultaneously.

Previous renal functions of the patients in the PET/CT group were evaluated according to the serum creatinine test performed for another reason and GFR levels in the last 6 months. The results of these tests were obtained from the local hospital registration system or the national patient data registry system (https://enabiz.gov.tr/). Written and verbal informed consent was obtained from all patients included in the study.

Data Collection

In addition to demographic data of the patients included in the study such as age, gender, body mass index (BMI), additional diseases, history of previous COVID-19, virus positivity rates in urine and renal involvement in PET/CT were determined and reported.

PET/CT images were reviewed and interpreted by the nuclear medicine specialist (A.T.) included in the project team. All urine COVID-19 PCR tests were also performed by the same microbiologists (S.G., O.M.P.).

The data used in the study were obtained from the Erciyes University Hospital Imaging-Automation System and patient follow-up cards created with the data obtained from the patients.

Nucleic Acid Extraction and RT-PCR

Nucleic acid extraction in urine samples was performed by using EZ1 virus mini kit v2.0 (Qiagen, Hilden, Germany) with automated EZ1 Advanced XL system (Qiagen, Hilden, Germany). Reverse transcriptase-PCR (RT-PCR) method was used for investigation of SARS-CoV-2 RNA in extracted samples. Genesig real-time PCR detection kit for SARS-CoV-2 (Primerdesign Ltd, Chandler's Ford, UK) and Oasig OneStep RT-qPCR master mix (Primerdesign Ltd, Chandler's Ford, UK) were used in accordance with the recommendations of the manufacturer. Positive and negative controls were included in the study and the amplification process was performed on the Rotor-Gene Q (Qiagen, Hilden, Germany) device.

Statistical Analysis

The distribution characteristics of the data were determined according to the Kolmogorov-Smirnov test and Histogram graphics. Normally distributed numerical data were expressed as mean ± standard deviation, numerical data not suitable for normal distribution were expressed as median (1-3. Quarter), and categorical data as numbers and percentages. Numerical data of dependent groups showing normal distribution were compared with paired samples t-test. The p-value less than 0.05 was considered statistically significant.

Results

A total of 66 patients were included in the study. PET/CT was performed in 6 of these patients simultaneously

with the urine sample. The mean age of the patients included in the study was 45.4±9.1 years, and the median BMI was 27.2 (24.4-28.8) kg/m^2. Thirty-six (54.6%) of the patients were male and 30 (45.4%) were female. All patients were symptomatic. It was found that 45 (68.2%) of these patients had COVID-19 lung involvement. While 12 (18.2%) of the patients whose previous data were available had normal renal functions 3-6 months ago (mean creatinine: 0.92±0.09 mg/dL), some impairment in these functions after COVID-19 infection (mean creatinine: 1.32±0.16 mg/dL). Patient characteristics have given in Table 1.

Table 1. Patient characteristics

Variable	Value (n=66)
Age (years)	45.4±9.1
Gender (Female/Male)	30/36
BMI (kg/m^2)	27.2 (24.4-28.8)
Base-line creatinine (mg/dL)	0.92±0.09
Duration of symptoms (days)	4.30±0.65
Fever (n, %)	24/66 (36.4%)

BMI: Body mass index

When the urine COVID-19 PCR results of 66 patients were examined, it was seen that only 1 (1.5%) patient had COVID-19 RNA positivity in the urine. It was found that the only patient with urine PCR positivity was a 69-year-old female patient, with lung involvement in thoracic tomography, and after 7 days of inpatient treatment, the patient was discharged with negativities in the throat swab PCR test and urine PCR test.

While renal functions were normal before, urine COVID-19 PCR test was not positive in any of the 12 patients with impaired renal function after COVID-19. PET/CT was performed in 6 of these patients who met the other inclusion criteria. Two (33.3%) of six patients were female and 4 (66.7%) were male. The mean age of these patients was 53.2±3.7 years. The creatinine values of the patients before and after COVID-19 were 0.78±0.07 mg/dL and 1.64±0.26 mg/dL, respectively (p=0.350). The patients' GFR values before and after COVID-19 were 92.66±5.00 mL/min/1.73 m^2 and 39.33±6.77 mL/min/1.73 m^2 (p=0.140). No evidence of pathological involvement in the kidneys was found on PET/CT in any of these patients.

Discussion

The COVID-19 outbreak, which started in 2019 caused by coronaviruses, still continues to be the first agenda item in the world as of 2021 (8). In some previous studies, it has been reported that coronaviruses can be detected in other systems and body fluids (9-13). In addition, it has been shown that the type of coronavirus that causes the COVID-19 epidemic can retain renal epithelial cells and tubular structures (9). In addition, renal involvement has been demonstrated by other histopathological and postmortem studies (14). Based on this information, coronavirus can be expected in the urine samples of some patients. However, today, the isolation of this virus from urine is still controversial. Wang et al. (12) performed PCR test by taking urine samples from 72 patients with positive COVID-19 PCR test in throat swab sample and they did not find COVID-19 positivity in the urine of any patient. Kim et al. (13) reported 2 of 247 urine samples (0.8%) and Peng et al. (15) reported in 1 (11%) of 9 urine samples positivity. In a recent review reporting the results of 780 studies and 8,136 specimens analyzed in these studies, it was reported that urine COVID-19 PCR positivity was not found in any patient with a positive nasopharyngeal COVID-19 PCR test (16). Except this, COVID-19 PCR positivity in urine has generally been limited to case reports (11).

In our study, only 1 (1.5%) of 66 patients known to be COVID-19 positive were found to have positive urine. In this context, it can be said that our results are consistent with the literature and the rate of detection of COVID-19 RNA in urine is quite low. In addition, the fact that the only patient with a positive urine PCR test was a patient with mild symptoms, normal renal functions, and clinical improvement in a short time, suggests that there is no correlation between urinary PCR positivity and disease severity.

Since the kidneys are the target of coronaviruses, PET/CT, which is a highly effective monitor of inflammation, showed kidney coronavirus involvement, which was an expected result for us. In line with this expectation, it has been previously reported that PET/CT may show involvement of other organs in COVID-19 (17,18). Therefore, our study is aimed to be the first study to show the efficacy of PET/CT in coronavirus renal involvement. For this reason, we applied PET/CT imaging to six patients whose renal functions were impaired without any other underlying cause and which we interpreted as COVID-19 kidney involvement. Interestingly, however, pathological involvement was not detected in any renal unit. Therefore, we believe that PET/CT is not an effective imaging method in the patient group we chose.

Study Limitations

Our study has some important limitations. First, the small number of patients included in the study is the most important limitation for our study. The second important limitation is that histopathological diagnosis methods were not used as an indicator of renal involvement

in our study due to ethical concerns. Instead, the use of serum creatinine and GFR values, which may vary depending on many factors such as dehydration and drug nephrotoxicity, may have caused partial errors in patient selection. Although various rates have been reported in the literature, up to 20% of false negatives have been reported in the first PCR test (19). The third limitation of our study is that a single PCR test was applied to urine samples. This may have caused diagnostic errors in the urine samples of some patients.

Conclusion

According to the results of our study, coronavirus genetic material was not found in the urine in nearly all patients with demonstrated active COVID-19 infection. The same is true for patients with impaired renal function and suspected urinary system involvement. In addition, the results of this study, in which we investigated the efficacy of PET/CT in urinary system involvement for the first time in the literature, showed that PET/CT is not an effective imaging method in urinary system COVID-19 involvement, although it is based on logical explanations.

Authorship Contributions

Concept: T.D., G.S., A.D., Design: A.D., S.G., A.T., O.Y., Data Collection or Processing: T.D., G.S., E.K., Z.T., Analysis or Interpretation: T.D., G.S., O.M.P., Literature Search: T.D., G.S., S.T.T., Writing: T.D., G.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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A Single Tertiary Center Outcomes on Cannulation Strategies and Extracorporeal Membrane Oxygenation in the Treatment of Respiratory Failure During COVID-19 Infection

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Abstract

Aim: Extracorporeal membrane oxygenation (ECMO) is an important option for the management of severe acute respiratory distress syndrome (ARDS) in Coronavirus disease-2019 (COVID-19) cases. We aimed to present our experiences of ECMO in patients with respiratory failure secondary to COVID-19.

Methods: Data of 22 consecutive COVID-19 patients with severe respiratory failure whom were supported with ECMO were collected from computer-based hospital software retrospectively. Patients were treated in a single medical center between April 23, 2020 and February 14, 2021. Patients were analyzed from the points of laboratory and inflammatory markers, ventilation and ECMO features.

Results: The ages of patients were between 30 and 69 years (mean age: 56.3±10.63). All patients were under maximum ventilator support, with the prone position. All patients had elevated levels of inflammatory indicators as D-dimer and ferritin. The mean level of ferritin was 1,564±1,611 ng/mL. D-dimer value was maximum 10.000 mg/mL (mean: 5,215±3,104), CRP increased to 177 mg/L (mean: 159±71). Percent of lymphocytes decreased as low as 2% (mean: 4.16±2.10). The mean duration of veno-arterial (VA) ECMO was 1.6±0.94 days whereas, for veno-venous (VV) ECMO, it was 10.05±5 days. VA ECMO was decided due to cardiovascular collapse. Four patients with VA ECMO survived a maximum of 3 days. Four of (22.22%) of 18 VV ECMO supported patient's blood gas values were at normal ranges, 3 of them needed tracheostomy, and all of could be discharged from the hospital.

Conclusion: Although, ECMO support for severe respiratory failure patients with COVID-19 is more challenging than regular ECMO applications, especially VV ECMO usage should be reminded as a remedy.

Keywords: COVID-19, extracorporeal membrane oxygenation, multi-organ failure

Introduction

The novel Coronavirus disease-2019 (COVID-19) induced disease (COVID-19) causes a rapidly evolving pandemic infection (1). The clinical findings of COVID-19 include high fever, dry cough, fatigue, pain especially at the back, diarrhea, and bilateral pneumonia, which can expand into acute respiratory distress syndrome (ARDS), metabolic acidosis, septic shock, coagulopathy, and hemorrhagic-septic multi-organ failure. Cytokine storm and hyper inflammation appear to be major components of severe COVID-19 pneumonia and multi-organ failure (2,3). The duration and severity of COVID-19 pneumonia and the time for improvement are currently not defined (4). There is not any approved treatment protocol except supportive care (5). The COVID-19 has begun to spread in Turkey by March 2019 (6).

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The percentage of hospitalized patients who required extracorporeal membranous oxygenation (ECMO) due to COVID-19 associated ARDS was reported as 2.8% on preliminary reports from China (7). The treatment of severe respiratory failure with ECMO needs expertise and skills (8). The number of patients who present to hospitals for ECMO annually is positively associated with the survival rate of the patients. WHO interim guidelines on the management of suspected COVID-19 recommend supporting with veno-venous (VV) ECMO to appropriate patients with ARDS related to COVID-19 in skilled centers with sufficient case volumes and clinical expertise (4). COVID-19 pneumonia in severe cases with low blood oxygen saturation may disturb hemodynamic values and causes multi-organ failure, so in these cases; ECMO may be the last life-saving tool. But of course, it is not the main treatment method of conventional ARDS as moderate positive end-expiratory pressure (PEEP), low tidal volumes and restricting plateau airway, and mild hypercapnia are among the first order management strategies. The addition of ECMO to treatment was based on the severity of respiratory failure despite protective ventilation and prone position of patients in deterioration of clinical findings despite appropriate treatment (7,9).

In the current research, we present our experiences with VV and veno-arterial (VA) ECMO support in the managing of patients with COVID-19.

Methods

Study Design

Ethics committee approval was obtained from the Istanbul Medipol University Ethics Committee (date: 02.18.2021, approval number: 179) for the retrospective analysis of the respiratory failure of COVID-19 patients treated with ECMO. All the patients were informed at the time of hospitalization and consent forms were signed by the patient(s) as well as a legally authorized representative.

The selected patients for ECMO application were evaluated by a trained team consisting of pulmonary diseases, Anesthesiology, Intensive Care, Cardiac Surgery, and Infectious Diseases experts.

Data were collected retrospectively through computer based hospital system from 22 patients with COVID-19 who had severe respiratory failure and were supported with ECMO. The diagnosis of COVID-19 confirmed using polymerase chain reaction (PCR). Patients were treated in a single medical center from April 23, 2020 to February 04, 2021. Regarding VV or VA ECMO, patients were divided into two groups as Group 1 and Group 2. Patients' comorbidities were evaluated regarding Charlson Comorbidity index (CCI) (10). Aggressive mechanical ventilation with a peak airway pressure of higher than 30 cm H_2O and fraction of inspired oxygen (FiO_2) higher than 0.8) for more than one week was accepted as an indication for ECMO. Severe comorbidity as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue diseases, previous ulcer diseases, liver diseases, hemiplegia, severe renal diseases, diabetes with end-organ damage, any tumor state, leukemia, lymphoma, metastatic solid tumor, AIDS and multi-organ failure, sepsis, and age above 75 years were used as contraindications for VV or VA ECMO application.

ECMO Application

All patients had severe lung damage. They were fully anesthetized and received mechanical ventilation. So, there was no need for local anesthesia for peripheral cannulation. Cannulation strategies for VA ECMO were from the femoral artery and vein whereas dual-stage right atrium-to-inferior vena cava cannula with the aid of echocardiogram or femoral and internal jugular veins cannulations were for VV ECMO. The cannulation techniques and the decision of weaning off ECMO were shown in the research flow diaphragm.

Statistical Analysis

The data analysis was arranged by software Statistical Package for Social Sciences, SPSS 20.0. Descriptive statistics and percentages for categorical variables, means, and standard deviation were used to evaluate the clinical and demographic characteristics of the patients. Categorical values were evaluated with "the chi-square test," and parametric values were evaluated with "independent samples t-test". Correlation analysis was evaluated by Spearman rank and Pearson correlation coefficients. $P<0.05$ was considered statistically significant.

Results

Care with ECMO was performed in 22 consecutive patients between the ages of 30 and 69 years (mean age, 56.3±10.63). While 16 of patients were male (72.72%), 6 of the patients were female (27.27%) (Table 1). In the medical history of patients, there was no known history of hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic atherosclerotic heart disease, venous thrombosis, or chronic renal disease. CCI was lower than 3 in all of the patients.

All patients reached maximum ventilator support, with 100% FiO_2 and placed in a prone position. Pre-ECMO; all the patients required high doses of vasopressors, mean inotropic scores reaching 36.4±5.9. BUN and creatinine levels were within the normal range at the time of hospitalization. All patients had meaningfully elevated

Table 1. Demographic data and ECMO duration				
		Group 1 (VV ECMO) (n=18)	Group 2 (VA ECMO) (n=4)	Total (n=22)
Age		56.7±10.7	59±11.1	56.3±10.6
Sex	Male	13 (72.2%)	3 (75%)	16 (72.7%)
	Female	5 (27.7%)	1 (25%)	6(27.2%)
Weaned of ECMO		4 (22.2%)	-	4 (18.1%)
Mean duration of ECMO/day		10 ±5	1.6±0.9	8.5±5.5
Erythrocyte infusion per day (mL)		437±29	600±74	466±76

ECMO: Extracorporeal membrane oxygenation, VV: Veno-venous, VA: Veno-arterial

levels of inflammatory indicators, such as D-dimer and ferritin, before ECMO use. The mean ferritin level was 1.564.08±1.611.90 ng/mL (minimum: 338, maximum: 7.000). D-dimer value was a maximum of 10.000 mg/mL (mean; 5215.15±3104.75), CRP increased to a maximum of 177 mg/L (mean; 159.81±71.25). Percent of lymphocytes decreased as low as 2% (4.16±2.10). The mean time from intubation to ECMO was found as 9.33±4.28 days. The mean duration of VA ECMO was 1.6±0.94 days whereas, for VV ECMO, it was 10.05±5 days. VA ECMO was decided due to cardiovascular collapse despite high doses of inotropic support (mean inotrope score: 64.2±16.5). Four of the patients with VA ECMO survived a maximum of 3 days and unfortunately lost. These patients needed high doses of inotropic agents and a mean of 600±74 mL of erythrocyte infusion per day. The needed rate of erythrocyte infusion for VV ECMO patients was 437±29 mL per day. Four of 18 patients with VV ECMO support could be weaned off ECMO after gradually decreasing flow and oxygen support from ECMO. Unfortunately, the remaining patients with VV ECMO were lost while still on ECMO. Among the patients who could be weaned off ECMO, one of them died due to cardiac rhythm disorders and hypotension on the post-ECMO 5th day. In all patients, conventional lung-protective ventilation as mentioned before was sustained during ECMO support and maintained in the four weaned patients on the first day after ECMO cessation. The level of PEEP was gradually decreased during weaning from ECMO and afterward during weaning from mechanical ventilation. After improvement of lung functions (FiO_2 <0.5, PEEP <10 cm H_2O, peak inspiratory pressure in pressure-controlled ventilation <25 cm H_2O), ECMO flow was gradually reduced lower than 2.0 L/min.

Computed tomography scans indicated generalized ground-glass appearance and consolidations decreased.

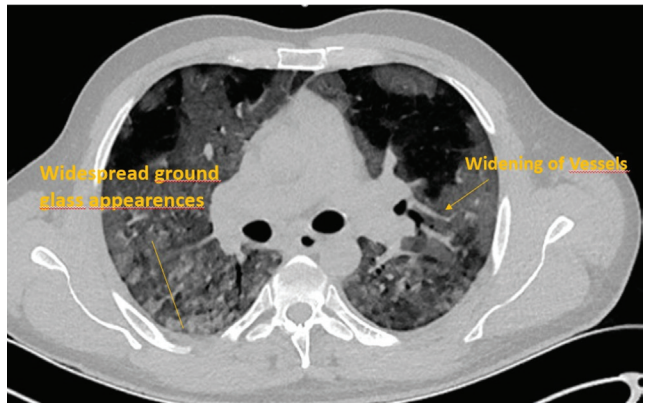

Figure 1a. Pre ECMO-Lung computerized tomography
ECMO: Extracorporeal membrane oxygenation

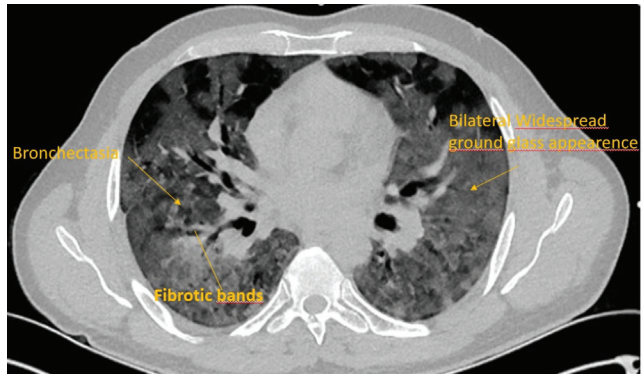

Figure 1b. Pre ECMO-Lung computerized tomography
ECMO: Extracorporeal membrane oxygenation

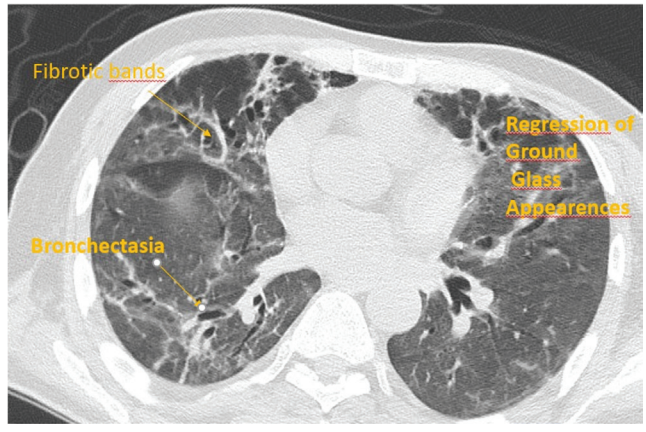

Figure 2a. After weaning off ECMO computerized tomography
ECMO: Extracorporeal membrane oxygenation

Figure 1a and 1b indicate the pre-ECMO findings and Figure 2a and 2b are post-ECMO findings. While four of 22 patients (18.18 %) weaned off ECMO, the ratio was 22.2% (4 of 18 patients) for VV ECMO supported patients. Their blood gas values were at normal ranges but due to long intubation duration and increased secretion, three

of them needed tracheostomy and they were discharged from the intensive care unit (ICU) to the ward with a tracheostomy cannula.

Among the 4 weaned off ECMO patients, 3 could be discharged from the hospital within the third week without any neurologic or ischemic sequela. Patients scheduled for ECMO treatment research flow diaphragm is added as Figure 3.

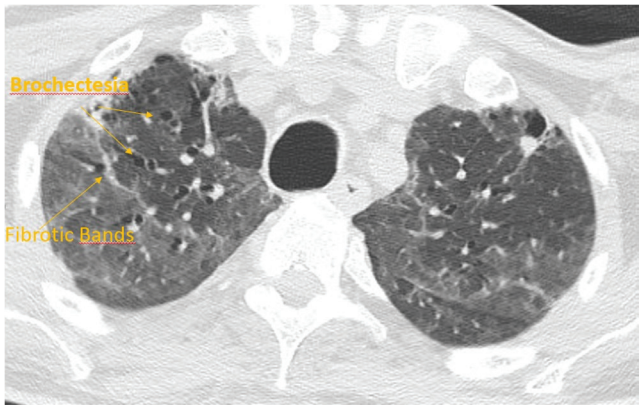

Figure 2b. After weaning off ECMO computerized tomography
ECMO: Extracorporeal membrane oxygenation

Discussion

The pathophysiology of respiratory failure in Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is due to massive alveolar damage. The ARDS rate of hospitalized patients range between 15% and 30% (7). Although in patients with COVID-19 pulmonary failure is expected primarily, there may be numerous patients requiring VA ECMO support. The underlying causes may be potential primary cardiac involvement that causes arrhythmias or myocarditis and the development of consecutive circulatory failure due to increased thromboses. A combination of increased thromboses with severe systemic inflammation increases the risk of atherosclerotic plaque disruption and acute myocardial infarction (11,12).

ECMO is a useful device especially in advanced cases of cardiac and respiratory failure. ECMO treatment in patients with COVID-19 is not fully established. The severity of lung damage also affects ventilation time, and immobility may restrict its benefits. All ECMO centers should have

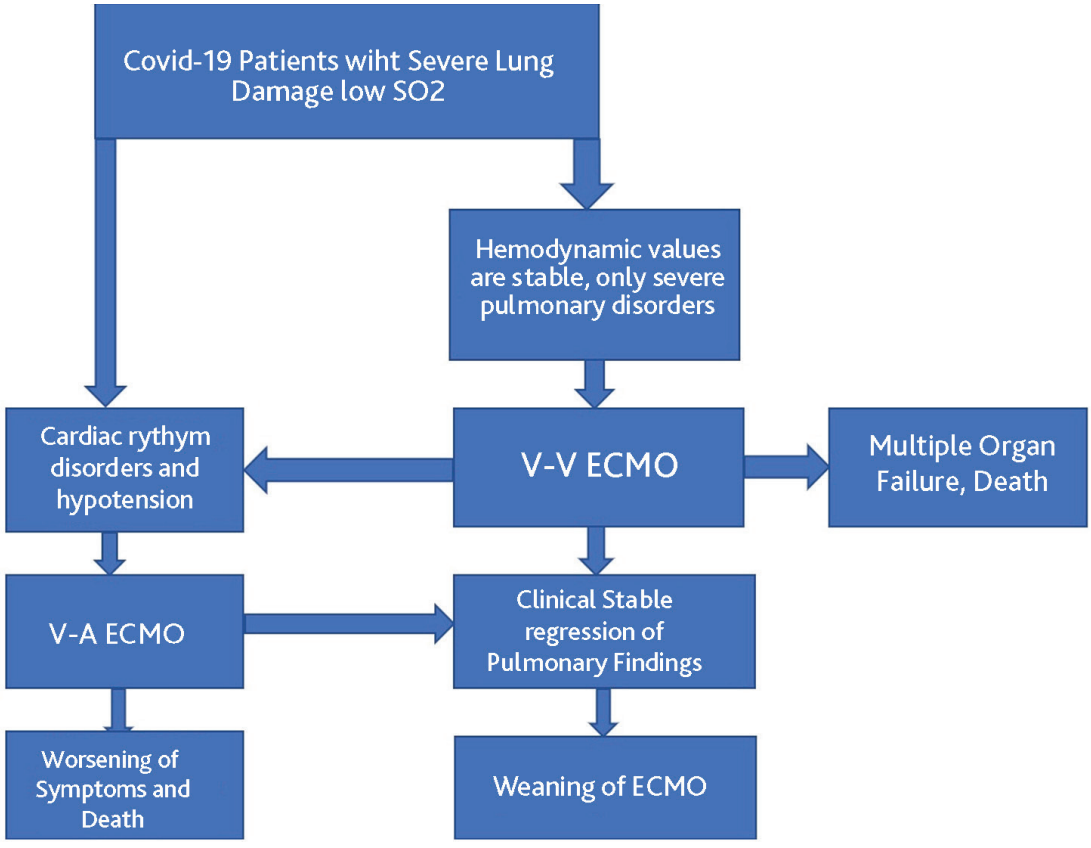

Figure 3. Research flow diaphragm

ECMO: Extracorporeal membrane oxygenation, COVID-19: Coronavirus disease-2019, VV: Veno-venous, VA: Veno-arterial

guidelines for ECMO application and weaning off protocols, and also supplementary team members as anesthesiology, cardiovascular surgery, thoracic and respiratory experts, infectious diseases experts should be involved in the management of treatment. Following satisfying weaning off ECMO, patients should be decannulated without any major complications, and respiratory and physical rehabilitation should be implemented with the use of Personal Protective Equipment (4). Moreover, outcomes with ECMO may be affected by several variables, as the rate of recovery of the pulmonary disease, secondary infections, and the effectiveness of antiviral drugs. In addition to conventional intensive care practices and sterility and infection management protocols, careful patient selection should be among the principles of care (3,4,13).

Cardiac rhythm and myocardial function evaluation have priory in the decision of VV or VA ECMO (14). In our cases, 3 of the patients had rhythm disorders and hypotension which made us decide to support these patients with VA ECMO. In one case, hypotension developed after VV ECMO support and we switched from VV to VA ECMO by cannulation of the femoral artery. Unfortunately, this patient was also lost due to cardiac rhythm disorders and septic cardiogenic shock.

Due to severe and bilateral lung damage in critically ill patients with COVID-19, patient selection for ECMO need to be careful. The factors that influence outcomes of patients like age, comorbidities, and multiple organ failure should be strictly considered especially in a situation of pandemics with limited trained personnel and sources as ECMO, ICU beds, and blood and blood products. In addition to careful patient selection, conventional intensive care management and infection control protocols should be among the primary priory of care (4). In our cases mean age of patients was 56.33±10.63 years and the range was 30-69 years. Also, in our clinic previously known coronary artery or rhythm disorders, renal and pulmonary dysfunctions or chronic pulmonary diseases were exclusion criteria for ECMO application in this particular patient population with COVID-19 associated ARDS. All of the patients were controlled by infectious diseases and CRP and ferritin levels were checked and routine cultures as tracheal aspirate, urine, and blood were investigated if he or she had fever. Anti-biotherapy was arranged according to the culture results for secondary infections such as *Staphylococcus aureus, Acinobacterium* or yeast.

Chronic kidney disease is associated with progressive illness or even death in COVID-19 as a comorbidity factor. But also, ECMO and COVID-19 are independent risk factors for acute kidney failure. However, for an effective management strategy, identification of the pathophysiology underlying renal manifestations of COVID-19 is needed. Monitoring of markers of kidney functions is also helpful in the identification of patients who are at high risk for worse outcomes during ICU follow-up for COVID-19 (15). Hemodialysis and hemofiltration were performed in 19 of 22 cases in our cohort although they had no known previous renal disease and their renal markers as BUN and creatinine were at normal ranges. Due to acidosis and low blood pressure, urine output decreased and creatinine values increased, so we needed to support these patients with renal replacement therapy alternatives.

Lymphopenia is also one of the effective and reliable findings to indicate the severity and hospitalization in COVID-19 patients (1). In our cases also lymphocyte count was meaningfully lower and the mean percent of lymphocytes were 4.16±2.10 (normal range: 22-40). Together with the decrease of the symptoms, with an inverse relationship, the number of lymphocytes increased.

In our cases, we aimed to choose VV ECMO at first in contrary to VA ECMO. In VV ECMO support the patient's erythrocyte transfusion need was lower than VA ECMO. And low transfusion requirement also attenuated the transfusion-related lung injury. In another aspect, cardiac involvement also decreases the success of ECMO. In our cases, the duration of VA ECMO support was very low as patients were lost due to hypotension and serious rhythm disorders despite full ECMO support. So, we become to change our choice of patients to stable patients in the cardiac aspect.

Some of the limitations of outcomes in ECMO applied COVID-19 patients are increased immobility and catheter infections and for this reason the use of the right internal jugular vein via dual-stage cannula as a single-access. The advantages of this cannula are the direct arterial flow to right ventricle and then to the pulmonary artery, thus we may achieve better oxygenation and ventilation; more easily giving position in bed and early mobilization. Additionally, a single cannula also decreases the risks of complications or revisions (16). In this research, single-access, dual-stage cannula was chosen in two cases but, in these patients required adequate support for blood oxygenation could not be reached and the patient's oxygen saturation could not be increased above 90%. So, one of the patients was lost due to multi-organ failure and in another patient, we decided to switch cannulas to femoral and internal jugular veins and his blood gas measurements became to improve and he was weaned off ECMO. While four of 22 patients (18.18%) weaned off ECMO, this ratio was 22.2% (4 of 18 patients) for VV ECMO-supported patients and 3 of them

could be discharged from the hospital. Other patients were cannulated from the right internal jugular vein and the right femoral vein with ultrasonography guidance and we did not face with any complications with this catheterization strategy.

Study Limitations

The study has certain limitations. The retrospective nature of the research is one of the limitations. Another limitation is the relatively small cohort size. The COVID-19 affects multiple organs and the effects of ECMO cannot be predicted exactly as being retrospective with low patient numbers as in our small cohort sample. However, our aim was to present our single-center clinical experiences in this unique group of COVID-19 patients requiring ECMO.

Conclusion

Although, ECMO support for severe respiratory failure patients with COVID-19 is more challenging than regular ECMO applications, especially VV ECMO utilization yielded better outcomes and should be kept in mind as a remedy. The decision and application should be based on a teamwork approach to carefully choose the most suitable patients who will benefit the most from this invasive treatment option for better outcomes and increased success rates as well as in order not to harm otherwise recovering patients with conventional care measures.

Authorship Contributions

Concept: M.O.U., Design: A.K., Data Collection or Processing: N.K., Y.Y., Analysis or Interpretation: M.U., S.O., Literature Search: K.E., Writing: M.O.U., D.M.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Effect of the COVID-19 Pandemic on the Number and Diversity of Pediatric Burn Intensive Care Unit Cases: A Cross-Sectional Study

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Abstract

Aim: The Coronavirus disease-2019 pandemic has effects on the healthcare system, as well as on the care of child burns. In our study, we aimed to compare the numbers and demographic data of patients who were treated and followed up during the pandemic period in our burn intensive care center with the data of patients in the same period one year prior.

Methods: The patients who were admitted to our tertiary pediatric burn center were divided into two groups: pandemic period (March 10-September 30, 2020) and pre-pandemic period (March 10-September 30, 2019). The groups were compared in terms of age, gender, city of origin, means of transport to the hospital, total burn surface area, burn etiology, duration of hospitalization, intubation status, and mortality from their medical records.

Results: In the pandemic period group, 414 children were admitted to the pediatric burn unit and 126 (30.4%) were hospitalized; however, in the pre-pandemic period group, 728 children were admitted to the pediatric burn unit and 98 (13.4%) were hospitalized ($p<0.01$). The average total burn surface area was s higher in the pre-pandemic group (16.31%) than in the pandemic group (12.29%). The intubated patient rate in the pandemic group (17.34%) was higher than the pre-pandemic group patients ($p=0.005$). The mortality rate was 3.1% in the pandemic group and 5.1% in the pre-pandemic group.

Conclusion: The rate of hospitalization to burn centers has increased in the pandemic period. However, patients in the pandemic period were mild cases compared to the pre-pandemic period.

Keywords: COVID-19 pandemic, COVID-19 lockdown, burn care, pediatric burns

Introduction

The novel Severe acute respiratory syndrome Coronavirus-2 and its Coronavirus disease-2019 (COVID-19) has rapidly developed as a pandemic and public health problem (1). The COVID-19 pandemic has placed immense pressure on the healthcare system.

Burns are a serious cause of trauma in all age periods and require emergency medical intervention (2). In children, burns are one of the leading reasons for hospitalization and may require intensive care. Low socioeconomic status, young age, low parental education, and overcrowding are known risk factors for burns (3). Our tertiary care pediatric hospital in the capital city is a pediatric burn referral center

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for all pediatric patients countrywide with 12 isolated pediatric intensive care rooms.

In the first COVID-19 wave, home isolation and curfew were implemented in many countries for decreasing social contact and preventing the spread of coronavirus infection (4). In our country, the public was restricted from taking to the streets between March 16 and May 30, 2020. During this period, schools were closed, and children were under curfew for nearly 16 weeks. Meanwhile, no restrictions were imposed on medical services. Although our hospital is a pediatric COVID-19 pandemic center, burn patients have not been restricted because they still need emergency interventions.

In our study, we aimed to compare the numbers and demographic data of patients who were treated in our burn intensive care center and followed up during the pandemic period with the data of patients in the same period one year prior.

Methods

The present study was approved by both the Republic of Turkey Ministry of Health COVID19 Scientific Commission (date: 08.12.2020, approval number: 874) and the Local Ethics Committee of Ankara City Hospital (date: 09.16.2020, approval number: E1-20-956). Our study is retrospective cross-sectional, therefore patient consent was not obtained. Pediatric burn patients who were admitted to our tertiary pediatric burn center during the pandemic (March 10 to September 30, 2020) and the pre-pandemic periods (March 10 to September 30, 2019) were included in our study. The patients were divided into two groups: the pandemic period and the pre-pandemic period. The groups were compared in terms of age, gender, city of origin, means of transport to the hospital, total burn surface area (TBSA), burn etiology, duration of hospitalization, intubation status, and mortality from their hospital medical records.

Cases that were admitted to our emergency department by their own parents and referred to our clinic with the 112 ambulance service for burns were evaluated. First, the burn areas of the patients were evaluated and dressed the wounds with protective equipment (Figure 1). Patients with indications for hospitalization were hospitalized to isolated single rooms in the burn intensive care unit. A symptom questionnaire was administered, and sampling for the COVID-19 polymerase chain reaction (PCR) test was performed on each patient admitted to the pediatric burn intensive care unit. The subsequent dressing and surgical procedures of the patients were performed in the operating room located in the burn center.

Statistical Analysis

Statistical analysis was done by using IBM SPSS 24.0 for Windows. Descriptive statistics (frequency, standard deviation, and average) were used in the evaluation of data. Kolmogorov-Smirnov and Shapiro-Wilk tests were done for determining the normal distribution. Age, TBSA, and hospitalization day distributions were not normal and non-parametric tests were done (Mann-Whitney U test) for comparing the groups. Pearson's chi-square test was done to determining the statistical significance of the differences between the averages of the groups in nominal values. The results were evaluated by a 95% confidence interval and $p<0.05$ significance level.

Figure 1. Wound dressing of a burn patient with protective equipments. It is published with the consent of the patient's parents.

Results

In this study, 224 burned children who were hospitalized and treated in our pediatric burn unit were categorized into two groups: the pandemic period group (who were under curfew due to the COVID-19) and the pre-pandemic period group. In the pandemic period group, 414 children with burns were admitted to the pediatric burn unit, and 126 (30.4%) children were hospitalized; however, in the pre-pandemic period group, 728 children with burns were admitted to the pediatric burn unit, and 98 (13.4%) were hospitalized ($p<0.01$). During the pandemic period, the COVID-19 PCR tests of two patients, one of them a 17-year-old girl and the other a 3-year-old male, were positive. The COVID-19 PCR results of other patients hospitalized in our center were found to be negative. The demographic data of the patients in the groups were detailed in Table 1.

When the patients were evaluated in terms of gender, the number of men was higher in both groups. The median age was 2.25/(0.50-18) years in the pandemic period group, it was 2.50 (0.3-16) years in the pre-pandemic

period group (p>0.05). The ratio of children aged 1-5 years was higher in both groups (Table 2).

The patients were also evaluated according to the city which they came from (Table 3). While the number of patients coming from Ankara was higher in the pandemic period group, the number of patients referred from the other cities was higher in the pre-pandemic period, and there was a statistically significant difference (p=0.04).

Patients were evaluated according to transportation to the hospital (Table 4). Although transport with 112 emergency ambulances services was more common in both groups, the rate of transport by private vehicle in the pandemic period group was statistically higher than pre-pandemic group (p=0.005).

Table 1. Demographic data of the groups of patients

	Pre-pandemic group (March 10-September 30, 2019)	Pandemic group (March 10-September 30, 2020)	p
Number of admitted patients	728	414	**0.001***
Number of hospitalized patients	98	126	**0.001***
Gender (male/female)	61/37	81/45	0.75*
Age (median/range)	2.50 (0.3-16) years	2.25/(0.50-18) years	0.53**
TBSA (median/range)	12.00 (1-75)	8.00 (1-70)	**0.03****
Duration of hospitalization (median/range)	11.00 (1-83) days	7.00 (1-75) days	**0.03****
Number of intubated patients	17 (17.34%)	7 (5.55%)	**0.005***
Mortality (%)	5 (5.10%)	4 (3.1%)	0.45*

*= Pearson's chi-square test, **= Mann-Whitney U test, TBSA: Total burn surface area

Table 2. Distribution of patients by age range

	0-1 years	1.1-5 years	>5 years	Total	p
Pre-pandemic group	23 (23.5%)	51 (52.0%)	24 (24.5%)	98	0.56*
Pandemic group	27 (21.4%)	60 (47.6%)	39 (31.0%)	126	
Total	50	111	63	224	

*= Mann-Whitney U test

Table 3. Distribution of patients according to the city of origin

Group	Ankara	Other cities	Total	p
Pre-pandemic	44 (44.9%)	54 (55.1%)	98	**0.04***
Pandemic	74 (58.7%)	52 (41.3%)	126	

*= Pearson's chi-square test. In the pandemic group, the number of patients from Ankara is statistically higher than the pre-pandemic group

The median TBSA was statistically higher in the pre-pandemic group (12%) than in the pandemic group (8%; p=0.03). Scald burns were the most common cause of burns in both groups. The distribution of the groups according to burn etiology was detailed in Table 5. There was no statistically significant difference between the groups in terms of burn etiology (p>0.05). The median duration of hospitalization was statistically higher in the pre-pandemic group (11.0 days) than in the pandemic group (7.0 days) (p=0.03).

Intubated patient and mortality rates of groups were given in Table 1. The intubated patient rate in the pandemic group (17.34%) was statistically higher than the pre-pandemic group (p=0.005). The mortality rate was 3.1% in the pandemic group and 5.1% in the pre-pandemic group (p>0.05).

Table 4. Distribution of patients according to transportation to hospital

Group	112 emergency ambulance	Private vehicle	Total	p
Pre-pandemic	75 (76.5%)	23 (23.5%)	98	**0.005***
Pandemic	74 (58.7%)	52 (41.3%)	126	

*= Pearson's chi-square test. In the pre-pandemic group, the patients transported by 112 emergency ambulance are statistically higher than the pandemic group

Table 5. Distribution of patients according to burn etiology

	Pre-pandemic group (March 10-September 30, 2019)	Pandemic group (March 10-September 30, 2020)	p*
Scald burns	69 (70.3%)	93 (73.7%)	0.32
Contact burns	3 (3%)	1 (0.7%)	0.20
Flame burns	13 (13.2%)	23 (18.2%)	0.46
Flame-inhalation burns	2 (2%)	1 (0.7%)	0.42
Electric burns	11 (11.2%)	7 (5.5%)	0.12
Chemical burns	1 (1%)	1 (0.7%)	0.85
Total	98	126	

*= Pearson's chi-square test

Discussion

The COVID-19 pandemic has altered the professional and personal lives of many individuals, especially health professionals. In our country, the first COVID-19 case was detected on March 10, 2020. On March 16, 2020, curfew restrictions were applied for children, and the schools were closed. During the pandemic, children mostly spent time at home with their families. As a result, with such changes in daily life, hospital admission patterns were affected.

A burn is a type of trauma that requires emergency intervention. Burn clinics have developed strategies for the COVID-19 pandemic in the treatment of patients with severe burns in general operating rooms and patients with stable, small, and uncomplicated burns as outpatients (5). It was reported that all burn patients who admitted to the hospital were screened for COVID-19 (5). During this period, we adopted the approaches shown in the literature for all burned patients who were admitted to our burn care center. Specifically, we took samples for COVID-19 testing from every admitted patient who was hospitalized at our burn center.

It was thought that in the lockdown period, family members would be at home so that children would have less risk of burning and would be more protected by family members. A variety of factors, including loss of social connections and family support, stress of working from home, and a lack of structured child care environments with reduced supervision of children, could cause severe burn injuries in children (6). There are many articles in the literature showing how pediatric burn centers have been affected during the COVID-19 pandemic. Studies from the UK and Morocco reported a 50% reduction in the number of patients in the period March-June 2020 compared to the same period of the previous year (7). In contrast, in Turkey and the United States, there was a significant increase in the number of pediatric hospitalizations due to burns during the COVID-19 pandemic (6,8). In a Brazilian study, it was shown that there was no difference in hospitalizations due to burns (9). In our study, it was observed that the number of patients who admitted to our center decreased at a statistically significant rate in the pandemic period compared to the pre-pandemic period ($p<0.01$), but the number of patients who were hospitalized and followed up increased statistically ($p<0.01$). In the pandemic period, the rate of patients referred from other cities was lower than in the pre-pandemic period ($p=0.04$). We think that the decrease in admission to our burn center in the pandemic period is due to the parents' not admit the children with mild burns to our center with fear of COVID-19 transmission. However, various factors, such as burn depth, burn percentage, circular extremity burn, socioeconomic reasons, and serious and infected burns that parents think they couldn't treat at home, may have played a role in the increase in the hospitalization rate.

In this study, we determined that the median of TBSA, the duration of the hospitalization of the patients, and the intubated patient ratio in the pandemic group were statistically lower than in the pre-pandemic group. In the pandemic group, although most of the patients were operated on, the duration of hospitalization was shorter, and early discharges were approved. In a similar study conducted in North Israel by Kruchevsky et al. (10) it was observed that TBSA and hospitalization rates did not increase. Reasonable scientific evidences for the increase in the number of burn deaths during the pandemic period were not found in the literature (9). Also, in our study, there was no statistically significant difference in the mortality rate between groups ($p=0.45$). So that, we should state that the COVID-19 pandemic does not affect the mortality of child burns.

It is known that boys are more exposed to burn trauma (11). In our study, we found that boys were more than girls in both groups, in accordance with the literature. In terms of gender, there was no statistically significant difference between the groups ($p=0.75$). Many studies have shown that the most common burns in children are between the ages of 1 and 5 (12-14). In accordance with the literature, in our study, it was observed that the patients' age were mostly between the ages of 1 and 5 in both groups. There was no statistically significant difference between the groups in terms of age ($p=0.53$) and age distributions ($p=0.56$).

Studies have shown that the majority of childhood burns are caused by accidents in the home environment (15,16). The most common place for burn injuries is the kitchen (15,16). Burns may occur in children mostly due to hot liquids (mostly hot tea in our country), including hot oil on the kitchen counters or hot tap water in the bathroom. Potential reasons for burn in children include reduction and loss of social relationships and family support, the stress of working from home, and lack of suitable childcare environments (6). When patients were evaluated in terms of burn etiology, we determined that scalds were the most common cause of burns in the two groups in this study. In the pre-pandemic group, we found that contact, and electrical burns were more common than they were in the pandemic group, however flame burns ratios were more common in the pandemic group. However, there was no statistically significant difference betwwen thee groups in terms of burn etiology ($p>0.05$). We can attribute the increase in flame burns in the pandemic period to the fact that children were spending more time at home due to the curfew.

In the study, we observed that the number of patients referred from other cities decreased, and the patients coming from Ankara for hospitalization mostly with their own vehicles in the pandemic period.

Study Limitations

Our study clearly has some limitations. It was retrospective and conducted in a single-center. Furthermore, the study period was limited to six months. However, despite these limitations, the study will contribute to the literature with aspects such as showing how pediatric

burns are affected by the COVID-19 pandemic and hence we are a pediatric burn reference center in our region, the variety and number of patients is high.

Conclusion

Compared to the pre-pandemic period, it was observed that the rate of hospitalization to our burn center increased in the pandemic period. However, it was determined that burned patients in the pandemic period were mild cases compared to the pre-pandemic period. The first reason for this increase is that burned patients who needed hospitalization were referred from other hospitals and pediatric burn units to our clinic, because they did not admit in the pandemic period. The second reason was that patients who were not hospitalized before but were followed up as outpatient, were hospitalized and isolated due to the risk of transmitted the COVID-19 infection in the control examination. In order to prevent this accumulation in future pandemic periods, treatment of burn patients should be provided in primary and secondary health care centers.

Authorship Contributions

Concept: H.C.O., S.K.Y., Design: M.N.A., E.S., Data Collection or Processing: M.E.O., T.J., G.K., Analysis or Interpretation: S.D., A.E., D.G., Literature Search: C.I.O., S.A.B., E.E.E., Writing: C.I.O., S.A.B., E.S.

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The Impact of Changing Processes in the COVID-19 Pandemic on Health Care Workers' Burnout Syndrome: Web-Based Questionnaire Study

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Abstract

Aim: Health care workers at the forefront of the Coronavirus disease-2019 (COVID-19) pandemic have faced increased workload and intense stress. It is essential to understand the relationship between specific processes that have changed due to the COVID-19 pandemic and the level of burnout of health workers. This study aims to determine health workers' perceptions regarding changing processes and burnout levels during the COVID-19 pandemic.

Methods: This study was carried out in a descriptive design. The research population consists of health workers who are actively working in Turkey. A web-based survey sampled 537 health workers who agreed to participate in the study. Research data was collected during dates between December 31, 2020, and January 10, 2021. This study measured health workers' perceptions of burnout and their experiences and attitudes during the COVID-19 pandemic.

Results: According to the findings of the study, 52% of health workers reported burnout. As a result of the regression analysis, we found that increased workload in nurses (B=1.12, t=0.56, p<0.05), failure to provide a safe work environment to physicians (B=1.04, t=2.28, p<0.05), increased mobbing on non-healthcare workers (B=0.74, t=2.31, p<0.05) and management vulnerabilities (B=0.71, t=2.02, p<0.05) had a positive impact on health care workers' burnout levels.

Conclusion: The changing processes in the COVID-19 pandemic have increased burnout rates in health professionals. Health care workers should be given the support they need to do their jobs, stay safe.

Keywords: Burnout, perception of health workers, COVID-19, work stress, health care professionals

Introduction

Burnout is a long-term and stressful psychological syndrome, many authors have analyzed this concept, and various models have been developed. Freudenberger first defined the concept of burnout in 1974 as the state of exhaustion caused by failure, wear, loss of energy and power, or unfulfilled desires in internal human resources (1). Maslach defined burnout as a syndrome of emotional exhaustion, desensitization, and inadequacy in individuals working with people of specific capacities (2). In Maslach and Jackson's most widely accepted conceptualization, burnout is considered a three-dimensional syndrome. These three dimensions are emotional exhaustion, desensitization, and personal success (3). Many researchers have researched burnout in different workplaces in the last 20 years (4,5). Burnout is defined as a psychological syndrome characterized as a negative emotional response to a person's work as a result of prolonged exposure to a stressful work environment. According to this definition, employees working in stressful occupations are more likely to develop burnout syndrome (6). Health care is listed among stressful occupations requiring intense personal interaction with people, especially patients and other health care providers. This situation paves the way for higher levels of stress and consequent burnout syndrome (7,8). Burnout is considered a severe problem among health care professionals (9,10). Burnout of health workers

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is essential because it will affect itself and the society in which it provides health care. Burnout may cause negative consequences on patient care provided by the health care worker (11).

The Coronavirus disease-2019 (COVID-19), which the World Health Organization considers a "pandemic," is a serious health problem facing humanity (12). Although health workers vary by country, they constitute an essential part of the people who contract the disease. According to some reports, health workers account for 14% of confirmed COVID-19 cases. More than 40,000 health workers have been established as COVID-19 positive in Turkey (13). It is known that health workers face numerous challenges at every stage of the pandemic. Even though studies have been carried out on anxiety and depression caused by the COVID-19 pandemic on society, very few studies have been conducted that show the psychological effects on health workers. Many trigger factors such as changing processes due to the burnout pandemic, increasing pressure, long working hours, administrative weaknesses, fear of carrying diseases to the immediate environment have increased burnout rates due to the burnout pandemic already expected in health professional groups (14,15).

Several studies have shown that physicians experience depression and anxiety that can trigger burnout due to the COVID-19 pandemic (16).

Burnout levels are likely to increase during the COVID-19 pandemic when health care workers face a high workload in providing health care. This increase is associated with a wide range of occupational stress factors that are likely to increase during the COVID-19 pandemic (17). Many of the health workers refused to work during the COVID-19 pandemic and quarantined themselves. This quarantine decision is due to the fear of infection. The constant fear of disease during quarantine and interruption of social support are critical factors that can affect burnout (18). In addition, many factors, such as lack of personal protective equipment, were associated with increased burnout and other mental health problems among health workers (19).

This study aims to determine whether the COVID-19 pandemic affects the level of burnout among health care professionals and the factors associated with it.

Methods

This study was carried out in a descriptive design. The web-based test method applied to 537 participants who agreed to participate in the research was used as a data collection method. Our research data was collected between 12/31/2020-10/01/2021. This study was carried out with participants living in different cities of Turkey who agreed to participate in the research. All participants provided informed consent for inclusion before they participated in the study. The survey was conducted anonymously, and all responses were optional. In this study, "Personal Information Form" and "Maslach Burnout Inventory (MBI)" were used as data collection instruments. The researcher's information form in our study consists of variables including participants' gender, age, institution type, profession, year of experience in the job, department studied, type of work, and questions about the perceptions of health workers during the COVID-19 pandemic.

Maslach Burnout Inventory

MBI was adapted to Turkish by Ergin (20) and reliability and validity analyses were performed. MBI consists of three subdivisions and a total of 22 substances: 9 substances of emotional exhaustion (EE), five senses of desensitization (DS), and eight substances of personal achievement (PA). The EE subdivision of MBI defines a person's feelings of being consumed and overloaded by his/her profession. The sub-dimension of DS is that the person acts without emotion and careless towards the people he/she serves. The PA sub-dimension defines a person's feelings of overcoming problems with success. After pre-application of the scale with a group of 235 people (physicians, nurses, teachers, etc.), some changes were made to the plate due to the analysis of the data obtained from the group. After the question items that make up the MTE were scored in the range of 0-4 points, each sub-scale was collected among itself, and three separate points were obtained. The EE and DS sub-dimensions of the 4-item Likert scale of 22 items were evaluated with a score of never=0, very rare=1, sometimes=2, most of the time=3 and always=4 points each. At the same time, in the lower PA dimension, scoring was conducted in reverse as never=4, very rare=3, sometimes=2, most of the time=1, and always=0 points. By collecting points for all sub-dimensions, scores were obtained ranging from 0-36 for EE, 0-20 for DS, 0-32 for PA, and 0-88 for MBI. In the EE and DS sub-dimensions, high scores indicate high burnout, and in the PA subgroup, the high score indicates an increase in burnout.

Ethical Aspect of the Research

This study received the non-interventional practices ethical committee decision no. E-20292139-050.01.04-427 dated 30/12/2020 by Sebahattin Zaim University Ethics Committee.

Results

Study Group

The study group of the study constituted 537 people, including 180 men and 357 women, between the ages of 18 and 65 (mage=35.73±10.13). The highest rate of the participants was 36.5% from the 2nd-tier public hospital,

nurses followed this rate with 44.1%, the average year of work in the profession was reported as 12.9±9.79%, the department in which they worked was notified as an outpatient with a rate of 32.2%, and participants said they worked without shifts with a rate of 54.7% (Graphic 1).

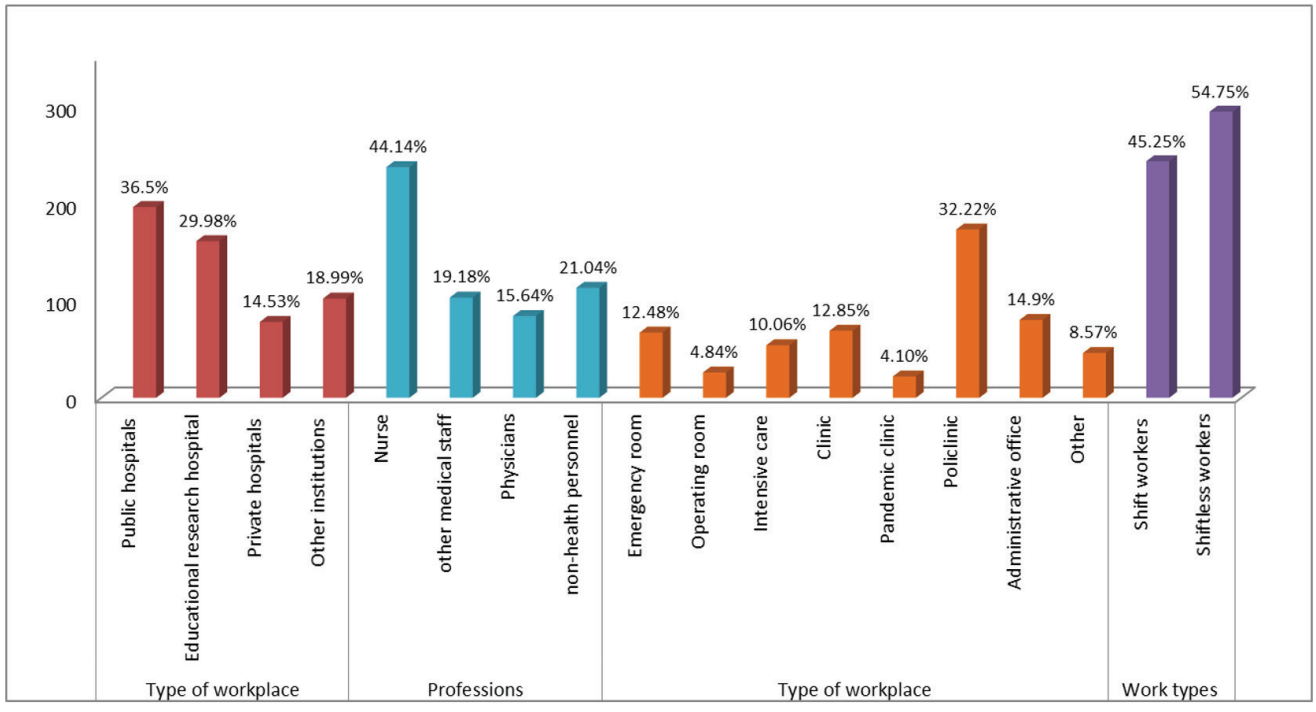
Statistical Analysis

Relationship Between Variables and Descriptive Statistics

Table 1 contains the average, standard deviation, kurtosis, skewness coefficients, and correlation coefficients between variables. The average age was found to be 35.73±10.13, while the total burnout average was found to be 51.80±7.85. Kurtosis values were between -0.59 and 0.19, and the skewness values were between -0.36 and 0.50. These values indicate that the variables exhibit a normal distribution. When correlation coefficients are examined, there is no significant correlation between the age of the participants and their burnout scores. In addition, while there was a negatively substantial relationship between the personal success sub-dimension and the EE and desensitization sub-dimensions, a significant positive association was found between the total burnout average and all sub-dimensions. There is also a positive, meaningful relationship between EE and desensitization.

Comparison of Burnout Levels by Demographic Variable

Independent samples were tested to compare burnout levels based on the gender of the participants. According to analysis results, there is a significant difference between EE (t=3.911, p<0.001), desensitization (t=3.407, p<0.001), personal success (t=-2.333, p<0.05) and exhaustion total scores (t=3.296, p<0.001) as per gender. While female participants' total scores from emotional exhaustion, desensitization, and burnout were found to be higher, the average of men in the lower dimension of personal success was found to be higher. When the impact size



Graphic 1. Socio-demographic characteristics of the participants

Table 1. The average, standard deviation, kurtosis, skewness coefficients, and correlation coefficients between variables

	X̄	SD	Skewness	Kurtosis	1	2	3	4
1. Age	35.73	10.13	0.50	-0.59	-	-	-	-
2. Emotional exhaustion	24.64	5.85	-0.36	-0.31	0.01	-	-	-
3. Desensitization	10.84	3.94	0.04	-0.53	0.04	0.64**	-	-
4. Personal success	16.33	5.01	-0.32	0.19	-0.08	-0.47**	-0.39**	-
5. Overall score	51.80	7.85	-0.29	-0.21	-0.02	0.77**	0.73**	0.09*
SD: Standard deviation								

of MBI and its sub-dimensions were examined by gender, it was determined that the effect was low (Cohen's d=0.2<d<0.5).

Independent samples were tested to compare burnout levels based on the work types of the participants. According to analysis results, there is a significant difference between EE (t=4.288, p<0.001), desensitization (t=4.471, p<0.001), and exhaustion total scores (t=5.781, p<0.001) as per work types. Emotional exhaustion, desensitization, and total burnout scores were higher among shift workers than those of shiftless workers. When the impact size of MBI and its sub-dimensions were examined as per work type groups, it was determined that the effect was low (Cohen's d=0.2<d<0.5).

One-Way analysis of variance was applied to compare burnout levels based on participants' professions. According to analysis results, there is a significant difference between EE (F=9.394, p<0.001), desensitization (F=6.226, p<0.001), personal success (F=2.805, p<0.05), and exhaustion total scores (F=7.260, p<0.001) as per professions. Lysergic acid diethylamide (LSD) test, one of the post-hoc tests, was performed to determine which groups had differences. As a result of the analysis, it was found that the average of emotional exhaustion, desensitization, and total burnout of physicians was lower than that of nurses and other health workers. In addition, personal success averages in physicians were higher than those of nurses and non-health personnel. Nurses had higher standards of emotional burnout and mass burnout than physicians and non-medical staff. Nurses have higher averages of desensitization than physicians and other medical staff while having lower average PA scores. The calculated value of $\eta 2$ for the occupation variable was less ($\eta 2$: <0.06 soft effect).

One-Way analysis of variance was applied to compare burnout levels based on participants' type of workplace. According to analysis results, there is a significant difference between EE (F=2.899, p<0.001), desensitization (F=6.125, p<0.001), and exhaustion total scores (F=6.910, p<0.001) as per to type of workplace. LSD test, one of the post-hoc tests, was performed to determine which groups had differences. It was found that employees in private hospitals had higher average EE scores, desensitization, and burnout than public hospitals, educational research hospitals, and other institutions. At the same time, it was found that the average desensitization of academic research hospital employees compared to employees of public hospitals and other institutions was lower. The calculated value of $\eta 2$ for the workplace variable was low ($\eta 2$: <0.06 soft effect).

Perception of Health Workers During the Pandemic Period and its Relationship With Burnout

Table 2 contains Pearson correlation coefficients (r) between health workers' perceptions and their burnout levels. When the perception of health workers is examined, it is seen that the highest value with an average of 9.77 is in the expression M3 ("I think the fear of carrying infections to our families has increased"). The lowest average is in the expression M2 with a rate of 6.54 ("I think violence has increased"). When the relationship between perceptions and the burnout levels of health workers is examined, it is seen that the burnout levels of nurses and non-health personnel in particular and all perceptions in Table 3 are positively significantly related. At the same time, there was a positive oriented significant relationship between burnout and the expression M5 ("I think a safe working environment cannot be provided"), M6 ("I think revolving capital practices are unfair"), M7 ("I think mobbing is

Table 2. The relationship between the perceptions of health workers and their burnout levels during the pandemic period

Perceptions	$\bar{X}$	SD	Burnout (r)			
			Nurse	Other health personnel	Physician	Non-health staff
M1. I think the fear of getting infected has increased.	9.36	1.23	0.14*	0.05	0.13	0.29**
M2. I think violence is on the rise.	6.54	1.77	0.22**	-0.08	-0.04	0.31**
M3. I think there is a growing fear of infection in our families.	9.77	0.81	0.25**	0.00	0.21	0.19*
M4. I think we do not spare enough time for our families and they cannot receive enough attention.	9.44	1.24	0.13*	-0.02	0.09	0.29**
M5. I think a safe working environment cannot be provided.	8.49	2.11	0.26**	0.21*	0.31**	0.43**
M6. I think revolving capital practices are unfair.	9.54	1.41	0.20**	0.25*	0.06	0.25**
M7. I think mobbing is increasing.	8.01	2.57	0.31**	0.22*	0.09	0.48**
M8. I think the management weakness is growing.	8.13	2.51	0.28**	0.30**	0.17	0.49**
M9. I think we have had to make some tough decisions.	9.01	1.54	0.18**	0.10	0.25*	0.42**
M10. I think the workload is increasing.	9.60	1.13	0.24**	-0.02	0.01	0.27**

*p<0.05, **p<0.01, SD: Standard deviation

increasing"). -M8 ("I think management weakness has increased") among other health personnel. A favorable oriented significant relation was found between burnout and only expressions M5 ("I think a safe the working environment is not provided") and M9 ("I think we have to make difficult decisions") among physicians.

Table 3 contains multiple linear regression analysis findings to examine the role of health workers' perceptions of burnout levels during the pandemic period. Collinearity, normality, autocorrelation, and multicollinearity assumptions were reviewed before moving on to regression analysis. For the collinearity hypothesis, only variables with a significant association in Table 2 were included in the regression analysis. Where the assumption of normality is met is presented in Table 1. Premises have been completed since the Durbin-Watson values for the autocorrelation assumption were between 1-3 and that the viral infectivity factor (VIF) values for the multilink belief were less than 10.

It is seen that the four regression analysis models in Table 3 are also significant. When the values obtained as a result of the regression analysis are examined, it can be seen that the expression M10 ("I think the workload has increased") positively predicts nurses' level of burnout. The expression M5 ("I think a safe working environment is not provided") entirely indicates physicians' level of burnout, and the expression M7 ("I think mobbing has increased"). M8 ("I think management weakness has increased") positively predicts non-health staff's level of burnout. It has been observed that the perceptions of other medical personnel during the pandemic period have no meaningful role in the story of burnout.

Discussion

The COVID-19 pandemic has affected lives worldwide, leading to unique challenges in all areas of life and all areas of medicine. With the pandemic affecting our lives in many ways, psychological resilience is a challenge that many will continue to face in the coming months. Many other potential triggers such as physical and social isolation, interruption of daily routines, financial problems, food insecurity, and stress are increasing due to the pandemic, creating a situation that threatens individuals' mental well-being and stability. The uncertainty brought on by the pandemic is also likely to increase the frequency and severity of mental health problems worldwide.

Burnout is a prevalent condition in health workers. Burnout levels are also linked to the development levels of countries. For example, in studies from high-income countries, the prevalence of burnout among health care workers ranges from 12.6% to 29.9% (21,22). In Tunisia, one of the low-income countries, the burnout rate was 68% in a study of nurses. Studies on the level of burnout of physicians have shown a high prevalence of burnout among general practitioners. They have shown that a third of physicians experience burnout at specific points during their careers. The burnout rate is even more pronounced among general practitioners. In a recent study in the United States, 45.8% of physicians reported at least one sign of burnout (23). Another research of more than

Table 3. The role of health workers' perceptions on burnout levels

	Nurse			Other health personnel			Physician			Non-health staff		
	Beta	SE	t	Beta	SE	t	Beta	SE	t	Beta	SE	t
Intercept	21.26	8.47	2.51*	26.67	9.39	2.84**	33.21	5.17	6.43***	27.65	5.96	4.64*
M1	-0.43	0.55	-0.79	-	-	-	-	-	-	0.87	0.46	1.89
M2	0.30	0.26	1.16	-	-	-	-	-	-	0.31	0.47	0.67
M3	2.02	1.12	1.81	-	-	-	-	-	-	-0.04	0.75	-0.05
M4	-0.62	0.57	-1.09	-	-	-	-	-	-	-0.01	0.51	-0.02
M5	0.13	0.27	0.47	0.53	0.46	1.15	1.04	0.46	2.28*	0.19	0.41	0.46
M6	0.32	0.71	0.45	1.46	0.98	1.49	-	-	-	-0.73	0.45	-1.62
M7	0.43	0.26	1.64	0.19	0.50	0.39	-	-	-	0.74	0.32	2.31*
M8	0.25	0.27	0.93	0.60	0.38	1.57	-	-	-	0.71	0.35	2.02*
M9	-0.07	0.42	-0.17	-	-	-	0.80	0.59	1.37	0.86	0.51	1.70
M10	1.12	0.56	1.99*	-	-	-	-	-	-	0.02	0.62	0.03
F (df)	F (10.226)=p<0.001			F (4.98)=3.596, p<0.01			F (2.81)=5.398, p<0.01			F (10.102)=6.093, p<0.001		
R, R2	R=0.40, R2=0.16			R=0.36, R2=0.13			R=0.34, R2=0.12			R=0.61, R2=0.37		
VIF	Between 1.33-2.33			Between 1.18-1.53			Between 1.15-1.15			Between 1.50-2.34		
Durbin-Watson	1,766			2,074			1,778			1,909		

*p<0.05, **p<0.01, ***p<0.001, SD: Standard deviation, VIF: Viral infectivity factor, SE: Standard error

500 physicians in the unıted Kingdom has revealed that at least a third of physicians experienced burnout (24). According to the study of health workers in Turkey, the overall burnout level varies between 35-38% (25,26). In another study of 820 physicians, 42% of physicians described themselves as exhausted, and 26% described themselves as partially bare (27). In this study, the overall burnout level was 51.8%.

The primary purpose of our study is to examine the effect of the COVID-19 pandemic on burnout syndrome, which is already common among health workers. Even if there are not enough studies on this subject yet in Turkey, assignments are available on this subject in the world when the field literature is examined. In a cross-sectional survey of 1,257 health workers working in 34 hospitals serving COVID-19 patients, a significant number of health workers reported experiencing symptoms of depression, anxiety, insomnia. The most affected were those who were particularly female and nurses who were at the forefront of providing nursing care to patients with suspected COVID-19 or directly engaged in providing nursing care to COVID-positive patients (28). Many studies have shown that the COVID-19 pandemic increased burnout in women as gender variables and in nurses on a professional basis (29-31). In this study, burnout scores were statistically significant in the COVID-19 pandemic in women in gender variability and nurses on a professional basis. These findings suggest that health care workers exposed to COVID-19 are at high risk of developing adverse mental health outcomes and may need psychological support or interventions.

The risk of infection is inherent in health care; it has always been and will continue to be for the foreseeable future. Therefore, effective infection prevention practices are essential both to ensure safety and to fight fear. Fear is a powerful emotion, and its impact on health care should not be underestimated. Health care workers are not immune to anxiety and fear, and in fact, levels of fear may be higher than in the general population. According to the results of this study, health workers were found to have a heightened perception of the fear of becoming infected and infecting their families. This perception is significantly higher in nurses and non-health personnel. Burnout symptoms increase as the fear of infection increases. It is thought that greater exposure of nurses and clinical support staff in patient care than physicians and other professional groups increases this fear. In the literature, it has been shown that the fear of infection and the fear of carrying the disease to their families are common in health workers in COVID-19 pandemics and previous pandemics (32,33).

Violence against health workers is a significant problem. Health workers think that the COVID-19 pandemic increases health violence. Considering the effect on burnout in our study, it is seen that it has a low level of impact. The study conducted by Elhadi et al. (34) and his colleagues has shown that there are increased violence cases, especially on physicians, during the COVID-19 pandemic. The results of the current study are also compatible with the results of this study.

Due to the increased workload during the pandemic process, long working hours, and fear of carrying the infection to their families and loved ones, health workers feel that they cannot spend enough time with their families and cannot meet their needs. Health care providers are hesitant to spend time with family members because of the risk of spreading the infection to their loved ones, and many health care providers isolate themselves at home. Similarly, social distancing makes it more challenging to communicate with friends. The closure of schools and daycare centers such as nurseries and kindergartens is becoming a significant challenge to find someone to care for the child, especially when the health care provider is a single parent or both parents are working. This situation is forcing health workers and causing them to feel that they are not taking care of their families enough. It is essential to get family support at this stage. The study of Shanafelt and his colleagues found that the need for family support from health workers was relatively high (9).

Another stressful factor for health workers who have to deal with many difficulties is working in a safe working environment. According to the results of this study, health workers consider that the environment in which they work is not sufficiently secure. However, health institution managers are obliged to take all measures regarding policies, programs, and practices that protect health workers from COVID-19 and provide open, consistent, transparent, and empathetic communication to all employees from management levels (35). Leaders demonstrate that the organization puts a high priority on employee health and safety, which creates accountability and employee support at all levels of the organization.

The COVID-19 pandemic creates multiple stresses on health care providers, including infection risk, social isolation, and economic consequences. One of these stresses is the financial losses of health workers. The COVID-19 pandemic has also caused several economic implications, such as reduced outpatient incomes and reduced salaries and benefits (36). In this study, we found the relationship between decreasing co-payments and distribution injustices and burnout.

The COVID-19 pandemic creates difficult interdependent decisions for health professionals and the individuals they serve. Findings involving COVID-19 risks raise questions that the professional community needs to

answer and respond to (37). One of the terrible features of the COVID-19 pandemic is that if the disease is not contained or delayed, the sudden increase of patients in need of intensive care will upset even well-equipped health systems. In such a scenario, health workers need to make difficult decisions, including who and how to allocate medical resources, which are already few. For example, who will stay in intensive care beds? Which patients face difficult decisions such as access to a limited number of ventilators (38). Decisions regarding the sharing of resources that arise in the context of COVID-19 are not limited to those directly related to patient care. Health managers may also have to decide the distribution of personal protective equipment for health care workers (39). The sense of fairness and ethical dilemmas make both health workers and health managers very difficult when allocating resources, i.e., making difficult decisions. The access of health workers to personal protective equipment throughout the world caused various difficulties in the early stages of the pandemic. This study has shown that it is very effective for health workers to make difficult decisions on burnout.

The rapid spread of the pandemic has led to increased workload in hospitals. COVID-19 patients are victims of the pandemic, but the second victim of this condition is health workers (40). It is natural for health workers working in such an environment to perceive this situation as mobbing. Since they have perceptions that mobbing is increasing, this is one factor that triggers/increases burnout. Health is a biological problem and a political, social, cultural, and economic problem. Therefore, countries' ability to manage COVID-19 is strongly influenced by their political-economic conditions, which can be considered both an advantage and a threat. This effect occurs on a country-by-country basis as well as on an institution-by-institution basis. Health systems are highly complex systems with structural vulnerabilities. Failure to design these systems well, failure to consider vulnerabilities, and poor health system functioning also cause health workers to be adversely affected (41). Business organization models do not act only as obligations imposed by others. These models serve as individual power mechanisms and mediate through subjectivity processes that suggest their style of action. Thus, health workers normalize their distress by assuming that the work expected of them is "what they need to do." It gives them the strength to cope. According to the results of this study, the perception that the pandemic is not well managed due to administrative weaknesses on an institution-by-institution basis exists in health workers, which affects burnout. A study in Ireland found that lack of government support by health workers, combined with cynicism, increases work-related stress and burnout (42). Work-related stress disproportionately affects health care workers (43). This situation occurs with excessive workloads, working in environments that require intense sensuality and where demand outweighs capacity. Many health professionals, who were at the forefront of the COVID-19 pandemic, faced many challenges, increased workloads, and stress, which made them vulnerable to exhaustion. Burnout is caused by increased work stress, increased time pressure, increased workload, and poor organizational support. These factors are pretty common despite their differences in health care and socioeconomic structure (44). As a result of this study, the perception of increased workload was naturally high, which is one of the factors affecting burnout.

In this study, the average burnout in the COVID-19 pandemic was 52%. When the field literature is examined, it is seen that health sector burnout rates range from 43% to 48% in previous studies (45). Suggests that the COVID-19 pandemic has increased the burnout of health workers in general. It is possible to find lessons in the literature showing that the COVID-19 pandemic is associated with many factors that increase the likelihood of health workers running out (46,47). In this study, these factors were found as follows: fear of infection, increased violence, fear of carrying diseases to their families, not being able to spend enough time and not seeing their families, not being able to provide a safe working environment, decreased wages they receive without additional payment, increased mobbing, management weaknesses and perceptions of having to make difficult decisions.

Burnout among health care workers can be reduced by health institutions, government, and non-governmental stakeholders targeting potentially modifiable factors. These could include providing additional educational opportunities and psychological support, strengthening institutional support for their physical and emotional needs, supporting family problems (e.g., childcare, transportation, temporary housing, fees), and providing adequate personal protective equipment. To prevent negative psychological consequences, mental health support for health care professionals is critical. Key interventions include access to psychosocial support, including web-based resources, emotional support line, psychological first aid, and personal care strategies.

Study Limitations

The current study has some limitations. First, it was limited in scope. Multi-center studies of this type of work in different countries will ensure better results. This study was conducted in Turkey, one of the countries moderately affected by the COVID-19 pandemic. Comparing this study with countries such as the United States, which

the pandemic has heavily influenced, will strengthen the study. Secondly, the study was carried out for ten days and lacked longitudinal follow-up. Due to the increasingly difficult situation, the mental health symptoms of health workers can become more severe. Therefore, the long-term psychological effects of this population are worth further investigation. The heterogeneity of the study group (nurses, physicians, other healthcare professionals) is a limitation.

Conclusion

In the COVID-19 pandemic, health professionals were anxious and faced excessive workload. In addition to the fear and uncertainty surrounding the control of the spread of the disease, unemployment, potential threats to meet the physiological needs of themselves and their loved ones, and numerous other biopsychosocial stress factors experienced can all pose a threat to the mental well-being of health professionals. In particular, high levels of stress and burnout reduce the psychological resilience of health workers. It is essential to assess the mental health of health care professionals and monitor the long-term effects of dealing with the COVID-19 pandemic. Burnout is thought to cause other persistent problems in the long run if not addressed early. In terms of continuity of health services during the COVID-19 pandemic, it is necessary to provide the required preventive and supportive services to protect the mental health and physical health of health workers.

Authorship Contributions

Concept: H.S., Design: H.S., A.B., Data Collection or Processing: H.S., B.K., Analysis or Interpretation: A.B., Literature Search: H.S., B.K., Writing: H.S., A.B., B.K.

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The Role of Youtube as an Information Source About Coronary Artery Disease During COVID-19 Pandemic

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Abstract

Aim: There are videos on Coronavirus disease-2019 (COVID-19) and coronary artery disease at various quality levels on Youtube. To investigate the quality of Turkish language videos on Youtube about COVID-19 and coronary artery disease.

Methods: The study was conducted between 1st and 3rd September 2020. Two doctors investigated keywords including coronary artery disease, COVID-19", "coronavirus, heart disease", "coronavirus, chest pain", "COVID-19, heartache" and "COVID-19, heart disease". "Coronary artery disease", "heartache", "chest pain" and "heart disease" are the Turkish translations for coronary artery disease, heart pain, chest pain and heart disease, respectively. Firstly, for each video, video length, number of days on Youtube, and the number of views and comments were recorded, along with the number of "likes" and "dislikes". Sources of the videos were categorized into three groups: "health care professionals", "new agencies" and "non-professional individuals". Moreover, DISCERN and medical information and content index (MICI) were evaluated.

Results: Finally, 92 Youtube videos met the study inclusion criteria. The present study included 36 informative videos, 34 patient experience videos and 22 news update videos, and none were categorized in the misleading group. The shortest video length was found in patient experience videos (p=0.001). The DISCERN scores of videos were 3.5±1.1 for informative videos, 1.8±0.4 for patient experience videos and 0.9±1.3 for news update videos. The statistical analyses revealed that informative videos had significantly higher DISCERN scores when compared to patient experience videos and news update videos (p=0.005 and p=0.001, respectively). The mean MICI score was 4.1±1.5 for informative videos.

Conclusion: The present study showed that videos about coronary artery disease and COVID-19 are generally poor quality and low reliability.

Keywords: Coronary artery disease, coronavirus, COVID-19, discern score, MICI, Youtube

Introduction

The coronavirus infection, which mainly affects the respiratory tract, has become pandemic, infecting almost 60 million between December 2019 and October 2020. (1). The World Health Organization declared coronavirus infection as a Public Health Emergency of International Concern, and many governments passed laws to prevent its spread, including international border closures, public transportation restrictions and the reassigning of general hospitals as specialist pandemic hospitals (2). Postponed outpatient appointments and difficulties in reaching professional health units led patients to seek medical information from other sources including newspapers, television and social media (3).

Online sources, including websites, e-libraries and social media are increasingly used as information tools in today's world. Freeman and Chapman (4) argued that video platforms are preferred information sources overwritten or audio texts. Youtube, a social media application established in 2005, now has video uploads in the billions (5). Previous studies revealed the importance of Youtube videos as information sources about the diagnosis, treatment and follow-up of various diseases. Kumar et al. (6) conducted a cross-sectional study of the content and accuracy of Youtube videos on hypertension, finding a significantly higher view rate for misleading videos. In another study, Bora et al. (7) revealed the poor quality of the information in Youtube videos about the Zika virus pandemic.

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Youtube management has no policy of conducting preliminary research on the quality of videos posted on the channel, thus videos can be categorized as containing information that is useful, inadequate or misleading. In the present study, we aimed to investigate the quality of Turkish language videos on Youtube about Coronavirus disease-2019 (COVID-19) and coronary artery disease.

Methods

Data Collection

The present study was approved by the Bezmialem University Ethics Committee (date: 10.04.2020, approval number: 2020-105). As no patient data were used in the present study, patient consent was not required. The study was conducted between 1st and 3rd September 2020. Two doctors (ES and CB) investigated keywords including "coronary artery disease, COVID-19", "coronavirus, heart disease", "coronavirus, chest pain", "COVID-19, heartache" and "COVID-19, heart disease". "Coronary artery disease", "heartache", "chest pain" and "heart disease" are the Turkish translations for coronary artery disease, heart pain, chest pain and heart disease, respectively. The data consisted of videos of between 2 and 15 minutes long. The video ranking system reveals that popularity increases for videos of at least 2 minutes, reaching their highest level at 15-16 minutes. Totally, 149 videos were found that met the length criteria. Videos with any language other than Turkish, and videos with irrelevant content were excluded from the study, leaving a total of 92 videos, which were recorded on a specific playlist, and carefully analyzed independently by two cardiologists.

Data Analysis

Firstly, for each video, video length, number of days on Youtube, and the number of views and comments were recorded, along with the number of "likes" and "dislikes". Sources of the videos were categorized into three groups: "health care professionals", "new agencies" and "nonprofessional individuals". Moreover, target groups were categorized as either "patients" or "healthcare workers". Four classifications were determined according to content, as follows. Videos which included accurate information about epidemiology, pathophysiology, symptoms, prevention methods and proven treatment alternatives were considered as an informative group. Videos with patients" stories of coronavirus were classified as personal experience group, and video news uploaded by news channels, as news update group. Finally, videos with misleading information were defined as personal propaganda.

Previous reports have used the DISCERN scores (from 0 point to 5 point) to achieve objective analysis about video quality, utility and reasonableness of information. The model included five yes/no questions. Each "yes" answer demonstrates a positive perspective, and counted as one point, "no" answers scored zero. Additionally, medical information and content index (MICI) was used to analyze the video content. The survey was scored for each video from 1 to 5, according to the content on disease prevalence, transmission information, clinical symptoms, screening and/or testing, and treatment results. Both authors used the survey mentioned above to determine the type, efficiency and quality of videos.

Statistical Analysis

Statistical analysis was done with the Statistical Package for the Social Sciences version 25.0 (SPSS IBM Corp., Armonk, NY, USA). Normality of distribution of the Variables was evaluated by Shapiro-Wilk test and Q-Q plots. One-way ANOVA test was preferred for comparison of the normally distributed variables, and non-normally distributed values were evaluated with Kruskal-Wallis test. Quantitative data are expressed as mean ± standard deviation values. Categorical variables were classified and analyzed using the χ^2 test or Fisher's Exact test. Post hoc analysis was done using the Games-Howell test. The Fleiss and weighted kappa (κ) were used to evaluate the inter-observer concurrence. The data were analyzed at 95% confidence level and p-value of less than 0.05 was accepted as statistically significant.

Results

The final analysis revealed that 92 Youtube videos met the study inclusion criteria. A total of 57 videos were excluded for various reasons: 7 videos were in languages other than Turkish, 8 had irrelevant content, and 42 had inadequate duration. The present study included 36 informative videos, 34 patient experience videos and 22 news update videos, and none were categorized in the misleading group (Figure 1).

Informative videos were most frequently watched, but difference was not statically significant (p=0.558). Similarly, duration of videos on Youtube, number of likes and dislikes, and number of comments were comparable between groups (p=0.244, p=0.804, p=0.953 and p=0.678, respectively). The shortest video length was found in patient experience videos (p=0.001). For the informative and news update categories, most were uploaded by news agencies, while only 22% of informative videos were uploaded professional health care individuals. Additionally, most patient experience videos were uploaded by nonprofessionals (p=0.286). The great majority of videos targeted patients: 88.9% of informative videos, 91.2% of patients experience videos, and 90.0% of news update videos (p=0.942) (Table 1).

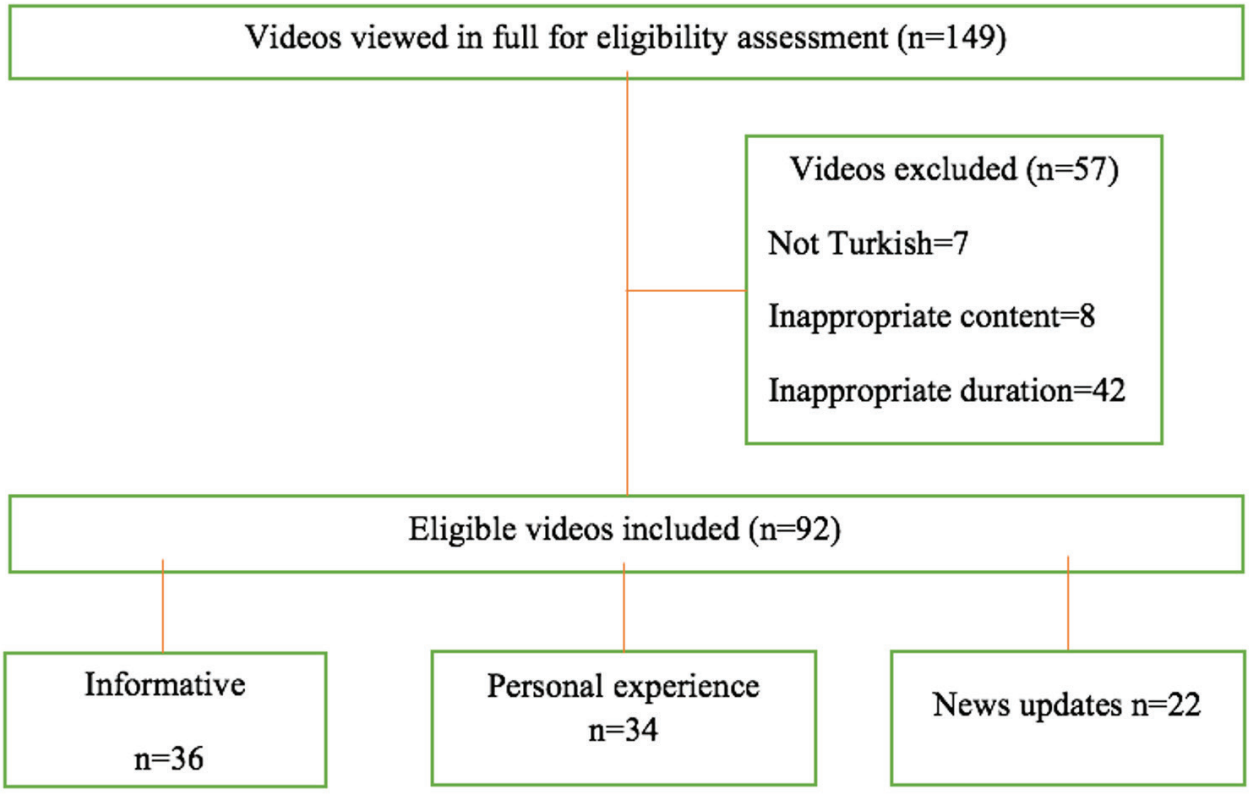

Figure 1. Flowchart of the study

Table 1. Analyses of video characteristics according to video type

Characteristics	Total	Informative	Patient experience	News update	p
Number of videos	**92**	**36**	**34**	**22**	
Audience interaction parameters					
Number of views, median (IQR)	201 (100-548)	176 (102-480)	243 (120-452)	215 (55-693)	0.558
Video length (minimum), median (IQR)	3.1 (2.3-4.3)	3.4 (2.7-4.9)	2.4 (2.1-3.1)	3.9 (2.4-5.0)	0.001[a]
Duration on Youtube (days), median (IQR)	135 (125-140)	136 (97-174)	135.5 (100-152)	131 (98-146)	0.244
Likes, median (IQR)	45 (21-118)	47 (19-107)	51 (20-187)	37 (25-71)	0.804
Dislikes, median (IQR)	0.5 (0-6)	0 (0-6)	1.5 (0-7)	0 (0-2)	0.953
Comments, median (IQR)	0 (0-2)	0 (0-4)	0 (0-4)	0 (0-1)	0.678
DISCERN score, mean ± standard deviation	2.6±1.5	3.5±1.1	1.8±0.4	0.9±1.3	0.001[b]
Source of upload	-	-	-	-	0.286
Professional individuals	20 (21.7%)	8 (22.2%)	9 (26.5%)	3 (13.6%)	-
Non-professional individuals	33 (35.9%)	12 (33.3%)	15 (44.1%)	6 (27.2%)	-
News agencies	39 (42.4%)	16 (44.4%)	10 (29.4%)	13 (59.1%)	-
Target audience	-	-	-	-	0.942
For doctors and healthcare providers	9 (9.8%)	4 (11.1%)	3 (8.8%)	2 (9.1%)	-
For patients	83 (90.2%)	32 (88.9%)	31 (91.2%)	20 (90.9%)	-

[a]: Video length was significantly shorter in the patient experience video group with One-Way ANOVA test.
[b]:DISCERN score was significantly higher in the informative video group with One-Way ANOVA test.
IQR: Interquartile range

The DISCERN scores of videos were 3.5±1.1 for informative videos, 1.8±0.4 for patient experience videos and 0.9±1.3 for news update videos. The statistical analyses revealed that informative videos had significantly higher DISCERN scores when compared to patient experience videos and news update videos (p=0.005 and p=0.001, respectively) (Table 2). Clinical symptoms and disease transmission information were the most frequently discussed content in informative videos (73.9% and 85.9%, respectively). Additionally, 32 videos and 15 videos, respectively, gave information about the prevalence of COVID-19, and about screening tests. The mean MICI score was 4.1±1.5 for informative videos (Table 3). The kappa coefficient of agreement regarding for DISCERN score was 0.81 (p<0.001) and for MICI score was 0.82 (p<0.001) (Table 4).

Discussion

Widespread internet usage has radically changed our daily habits regarding shopping, professional activities, and accessing information about disease (8). According to current Youtube statistics, 19 of 20 internet users watch Youtube videos (9). The COVID-19 pandemic highlighted the need to investigate the accuracy of Youtube videos about COVID-19 and cardiac disease, because the introduction of travel restrictions and difficulties in reaching the professional health care system meant that people were more likely to access such videos.

Previous reports proved and externally validated the usage of DISCERN score in the evaluation of video quality as an information source. The DISCERN score takes values between 1 and 5. Higher values indicate better quality of information content. Ferhatoglu et al. (10) investigated Youtube videos on sleeve gastrectomy, finding that content uploaded by professional health workers had significantly higher DISCERN scores. Similarly, for Youtube videos on pregnancy and COVID-19, Yuksel and Cakmak (11) found significantly better DISCERN scores for videos which were produced by health care providers. In accordance with aforementioned studies, we found significantly higher DISCERN score in informative videos in comparison with patient experience videos and news update videos (p=0.005 and p=0.001, respectively).

The MICI was first described by Nagpal et al. (12) to assess the video content quality during Ebola pandemic. The chart indicates that scores are awarded 1-5 points for each of five components: prevalence, transmission, clinical symptoms, screening/testing, and treatment outcomes of the disease. Although there is no cut-off value in the MICI score, higher values are associated with better content. Atac et al. (13) evaluated MICI scores of videos about the COVID-19 pandemic and found a 3.33 score for videos in Turkish and 2.76 for videos in English. In another study by Dutta et al. (14) a mean MICI score was 5.68 was found for videos in six different languages: Arabic, Bengali, Dutch, English, Hindi and Nigerian. Wide variations were found for MICI scores for videos about the COVID-19 pandemic in different studies, and we suggest that this is due to content quality improving over time. The present study is the first to evaluate the quality of Youtube videos about coronary artery disease and COVID-19, and the result was a MICI score of 4.1.

Previous studies about information sources in Youtube videos present conflicting outcomes. According to Atac's study, of all the useful medical videos on Youtube, most (76.1%) were shared by news channels, and only 8.7% by professional health care providers (13). In contrast, in Yuksel and Cakmak (11) study, 73.3% of informative videos were produced by physicians, and only 20% by new agencies. In our study, we did not find significantly different according to the source of video upload, and most of the informative videos were uploaded by new agencies. However, we believe that the increasing numbers

Table 2. Pairwise comparisons of video groups according to video type

Characteristics	p		
	Informative vs Patient experience	Informative vs News update	Patient experience vs News update
Video lenght	0.001[a]	**0.986**	0.001[a]
DISCERN score	0.005[a]	0.001[a]	**0.268**

[a]: Post-hoc analysis (Games-Howell test), Values of p<0.05 was accepted as statistically significant and marked bold

Table 3. Detailed content analysis of informative videos based on MICI scores

Component of MICI scale	Videos with information	MICI score*
Prevalence	32 (34.8)	0.9±0.5
Transmission	79 (85.9)	1.2±0.6
Clinical symptoms	68 (73.9)	1.0±0.6
Screening/tests	15 (16.3)	0.4±0.5
Treatment/outcomes	54 (58.7)	0.9±0.7
Total MICI score		4.1±1.5

*:Mean ± standard deviation, MICI: Medical information and content index

Table 4. The inter-observer agreement for DISCERN and MICI score

	κ coefficients	95% CI	p
DISCERN score	0.81[a]	0.76-0.85	**0.001[a]**
MICI score	0.82[a]	0.77-0.87	**0.001[a]**

[a]: There is very high agreement among observers, MICI: Medical information and content index, CI: Confidence interval

of Youtube videos by professional healthcare professionals will eventually improve the overall quality of the videos.

Study Limitations

The present study is novel in that it is the first to assess Youtube videos about coronary artery disease and COVID-19; nevertheless, there are some limitations. Firstly, we evaluated videos only in Turkish, without a comparison with videos in other languages. Additionally, after six months of the COVID-19 pandemic in Turkey, new videos containing the most recent information are being uploaded. The quality of videos produced during different stages of the COVID-19 pandemic may be the subject of another study. Lastly, we chose five keywords, however, the inclusions of other terms related to cardiac disease and COVID-19 would provide a greater range of videos.

Conclusion

Youtube videos are accessible and can be a valuable information source on coronary artery disease and COVID-19 for patients and their relatives. However, the present study showed that videos about coronary artery disease and COVID-19 are generally poor quality and low reliability. We believe that with greater efforts towards standardization and improvement, Youtube videos could become regarded as valuable information tools on COVID-19 possible effects on coronary artery disease.

Authorship Contributions

Concept: E.S., Design: E.S., Data Collection or Processing: C.B., Analysis or Interpretation: E.S., Literature Search: C.B., Writing: E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

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COVID-19 Associated Transient Cytotoxic Lesion of the Corpus Callosum: Report of Two Cases and Current Literature Review

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Abstract

Cytotoxic lesion of the corpus callosum (CLOCC) stems from a variety of causes such as malignancies, drug treatments, metabolic disorders, subarachnoid hemorrhage, and infections, and often presents as encephalitis or encephalopathy.

During this pandemic, we saw 2 cases with this lesion; the first one was a 42-year-old male who presented to the emergency department with complaints of headache, fever, and cough. There was a ground-glass opacity in the thorax computed tomography, and diffusion restriction was found in the corpus callosum splenium in the cranial magnetic resonance imaging (MRI) performed for headache that did not resolve with analgesic treatment during hospitalization due to the preliminary diagnosis of Coronavirus diseases-2019 (COVID-19) pneumonia. In the second case, Severe Acute Respiratory syndrome Coronavirus-2 polymerase chain reaction was found to be positive in the examinations performed during his admission to the emergency service due to weakness and presyncope, and diffusion restriction was observed in the corpus callosum splenium like the first case in cranial imaging. The follow-up cranial MRI was normal in both cases, so they were diagnosed with CLOCC.

We aimed to report the present cases with COVID-19 associated CLOCC since they presented only as a headache and a presyncope without any mental deterioration.

Keywords: COVID-19, splenium, corpus callosum, headache, presyncope

Introduction

Coronavirus disease-2019 (COVID-19) infection has a wide range of symptoms from mild such as coughing and fever to severe such as multiple organ failure, and it is known to have a mortality rate of 2-4% (1). A study conducted in the province of Wuhan where the outbreak spread from found that the neurological involvement was 36.4%, and that 35.9% of the patients with neurological involvement had headaches (2).

Cytotoxic lesion of the corpus callosum (CLOCC) is an imaging finding which usually resolves within the first month of the neurological symptom, and develops in a variety of medical conditions including viral infections, epileptic seizures, metabolic disorders, drug toxicity, malignancies, status migrainosus, and cerebrovascular disease (3). While the co-existence of this lesion with COVID-19 was shown, as in our cases, moderate-to-severe encephalopathy has been highlighted in the clinical pictures of most cases; therefore, we aimed to contribute to the literature with our cases having only a headache and a presyncope without any encephalopathy.

Case Report

Case 1

A forty-two-year-old male patient without any known chronic diseases presented to the emergency department in July 2020 with headache, fever, coughing, nausea-vomiting, and weakness for the past 3 days. In the

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emergency department, body temperature was 38.4 ˚C, blood pressure was 110/60 mmHg, respiratory rate was 18/minute, and the oxygen saturation was 93% on room air. When the computed tomography (CT) of the thorax revealed areas of parenchymal consolidation containing air bronchograms in the right upper lobe anterior segment, right lower lobe superior segment, right lower lobe medial basal segment, together with the infiltrations of ground-glass opacity in those areas, the patient was hospitalized with the preliminary diagnosis of COVID-19 pneumonia. Tests revealed high leukocytosis (white blood cell: 13.46 ref. 3.98-10.2 10^3uL), as well as high levels of markers of systemic inflammation such as C-reaktif protein (CRP) (235.7 mg/L, ref. <5), ferritin (919.1 ng/mL), fibrinogen (603 mg/dL), and D-dimer (10.15 mg/L, ref. <0.55). Nasopharyngeal swab gave a negative result for Severe Acute Respiratory syndrome Coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR). It was discovered that the patient about whom we were consulted for a headache had already been having moderate headaches responding to analgesics and lasting for 3 to 4 hours once a week, but the headache at the time of presentation was different from the previous ones and did not ease with analgesics. He described a persistent frontal lobe headache aggravated by coughing and caused by compression he defined as pressure. Having no other accompanying symptoms such as nausea, dizziness, photophobia, and phonophobia, the patient had normal neurological exam results, and his cranial CT gave normal results as well. When the severity of headache did not change following a symptomatic treatment of intravenous 1 g/d paracetamol, cranial magnetic resonance imaging (MRI) was used which revealed a nodular lesion with restricted diffusion in the middle part of the splenium of the corpus callosum. The patient whose headache had become less severe as the clinical picture of pneumonia improved and eventually disappeared completely by the time of discharge underwent another cranial imaging 1 month later for the follow-up of the lesion which was then found out to have disappeared (Figure 1).

Case 2

A fifty-eight-year-old male patient with no known history of any chronic disease presented to the emergency department in July 2020 with weakness, malaise, occasional coughs and presyncope present for the last three days. His body temperature was normal and oxygen saturation was 97% on room air in the emergency department. Thoracic CT scan revealed images of patchy infectious consolidations in the basal segments of both lungs. The patient was diagnosed with anemia and CRP was found to be 20 mg/L while procalcitonin was 0.09 ng/mL (ref <0.065 ng/mL). Having normal D-dimer and ferritin levels, the patient however tested positive for SARS-CoV-2 by PCR. The brain CT scan aiming to investigate a probable posterior circulation infarct revealed no pathologies other than cavum septum pellicidum while the cervical and cranial CT angiography revealed mild-to-moderate narrowing in segment V4 of the right vertebral artery. In the diffusion sequence, the MRI scan showed a lesion with restricted diffusion in the splenium of the corpus callosum, and the follow-up cranial MRI scan 2 days later revealed that the restricted diffusion in the splenial region had persisted, and the lesion was still present in the FLAIR sequence. Moreover, the T2-FLAIR sequence revealed bilateral multiple hyperintense millimetric regions with subcortical localization and the heme sequence showed several hypointensities consistent with hemorrhage. The follow-up MRI scan 5 days later detected a change in lesion signals consistent with the subacute stage. The EEG test investigating the etiology of presyncope in the patient revealed a basic bioelectrical activity comprising widespread low-amplitude fast waves in both hemispheres, but there was no epileptogenic activity. The follow-up cranial imaging 1.5 months later

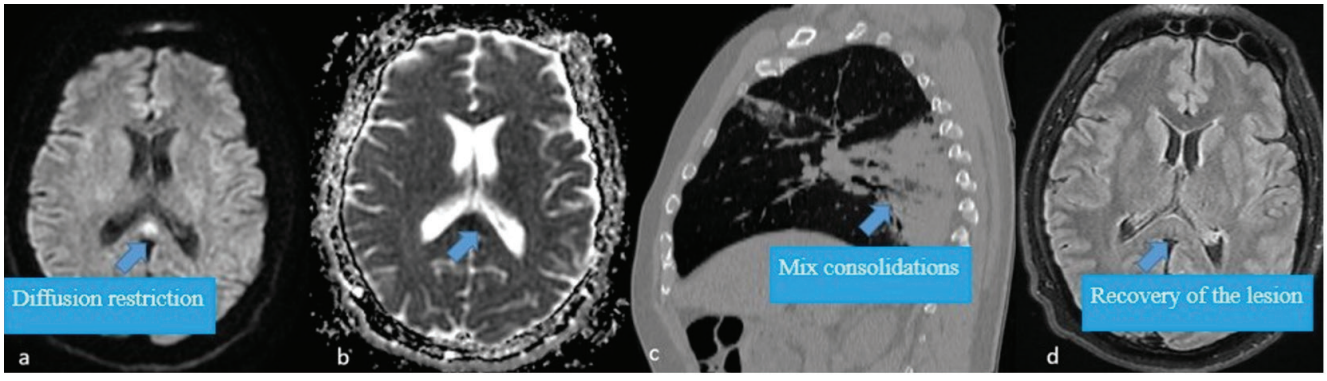

Figure 1. (a, b) Fourty-two years old, the male patient has diffusion restriction in the middle part of splenium (c) Mix consolidations in right upper and lower lobes with bronchograms in the sagittal reconstruction of thorax computed tomography mediastinal window (d) Recovery of the lesion in axial FLAIR sequence without any sequelae or signal 1 month (arrows)

revealed that the restriction of diffusion had disappeared (Figure 2). Written informed consent was obtained from the patient for publication of these case reports.

Discussion

CLOCC has been identified to be accompanied by various pathologies including medication-related problems, traumas, subarachnoid hemorrhage, malignancies, metabolic disorders, and most importantly, viral infections by some groups of viruses such as Adenovirus, H1N1 influenza, Epstein-Barr, and Rotavirus (4). While these lesions were previously identified as mild encephalitis/encephalopathy with a reversible isolated SCC lesion Middle East respiratory syndrome coronavirus, reversible splenial lesions, and reversible splenial lesion syndrome, later the term CLOCC was adopted since not all the cases had mild encephalopathies (they might be non-existent or severe), or they were not restricted only to the splenium (5). Involvement of the corpus callosum manifests itself in one of three models in radiological imaging, i.e. a small circular or oval lesion in the center of the splenium, a lesion centered in the splenium but extending to the adjacent lateral white matter along the callosal fibers, or a lesion found in the posterior region but extending to the anterior corpus callosum (4). This transient lesion which is always found in the center of the splenium in adults has been shown to exist in children as both a small lesion, as in adults, and a lesion extending throughout the corpus callosum and into the parietal white matter, and sometimes even into the frontoparietal white matter (6).

Examination of the pathophysiology of these lesions caused by systemic infection, as in our case, revealed that leukocytes produce proinflammatory cytokines and increase the permeability of the blood-brain barrier and thereby allowing the cytokines and inflammatory cells to enter the central nervous system (CNS). After that the CNS cytokines activate the glial cells (microglia, astrocytes and oligodendrocytes) causing cytotoxic edema through excitotoxic mechanisms (4,7). However, some lesions of the splenium of the corpus callosum secondary to COVID-19 have been shown to be of ischemic nature secondary to hypercoagulability (8). While focal infarction of the corpus callosum is rare since the corpus callosum receives its blood supply from three main arterial systems and there is a pericallosal anastomotic plexus, it is the most common site for the infarction of the splenium. In the acute stage MRI, it presents as diffusion restriction in DWI, high intensity in T2-weighted imaging, and low intensity in T1-weighted imaging. It is differentiated from CLOCC since gliosis and atrophy sites develop later and are permanent (9). In a case series of 73 patients with COVID-19 who were scanned retrospectively and underwent cranial MRI, the ratio of diffusion restriction in the splenium of the corpus callosum was determined to be 4.1% (3 patients), and two of these cases were interpreted to be ischemic. A follow-up MRI of one case on day 25 gave normal results which were interpreted as CLOCC (10).

As the number of cases, worldwide cases increased, retrospective studies on brain imaging have also increased. In a brain imaging study of 7 COVID-19 positive newborns hospitalized due to fever and feeding impairment in Italy, 6 of 7 cases was found a mild reduced diffusion in the genu and, in a lesser extent, in the splenium of the corpus callosum (11). In two different studies, they found that the microhemorrhages were the most common findings, one of our cases had multiple microhemorrhages as supporting these findings (12,13). In a retrospective review by Sawlani et al. (12) microhemorrhages were present in 60% of patients, with all these patients demonstrating microhaemorrhage in the splenium of the corpus callosum and the most common indication was delirium. In another study includes 16 critically ill patients with COVID-19 who underwent brain MRI because of coma or focal neurologic deficits, diffuse microvascular injury involving the subcortical and deep white matter was detected in 69% of patients. Microvascular lesions manifested as punctate

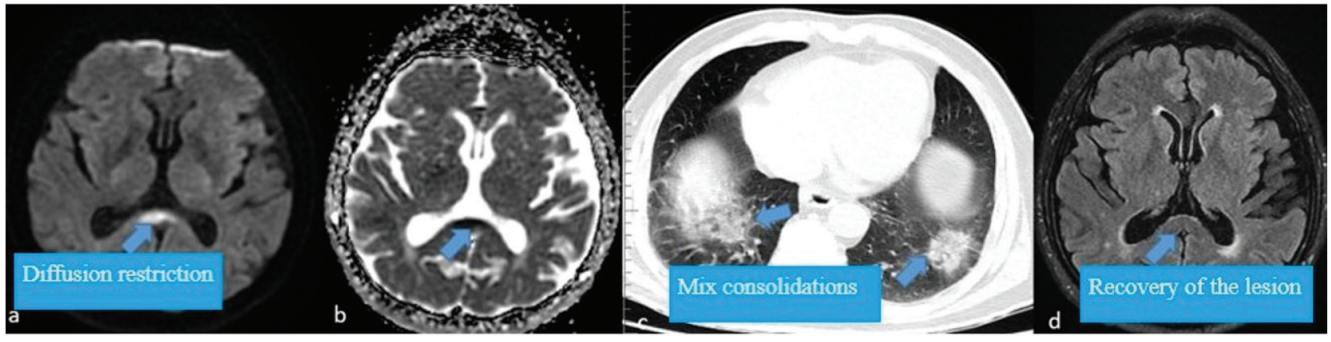

Figure 2. (a, b) Fifty eight years old, male patient with splenial diffusion restriction in DWI (c) Mix consolidations in bilateral posterior segments of lower lobes in axial thorax computed tomography mediastinal window (d) Completely regression of lesion in the axial FLAIR sequence of control cranial magnetic resonance imaging after one and a half month later (arrows)

and linear hypointense foci on susceptibility-weighted imaging, with a neuroanatomic predilection for the corpus callosum and the subcortical and deep white matter (13).

Literature review revealed a total of 14 cases of CLOCC secondary to COVID-19 5 of whom were pediatric patients and all had mental deterioration of varying degrees. Our cases are the first CLOCC cases reported without any mental deterioration.

Conclusion

CLOCC may have a variety of causes, the most important one being viral infections. It should be noted that COVID-19 is one of the causes of this lesion and may present without any mental deterioration, and ischemic stroke should be considered in the differential diagnosis.

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Authorship Contributions

Concept: G.G., N.G., Design: A.D.C., G.S., Data Collection and/or Processing: G.G., Z.M., E.Z., G.S., N.G., B.M.U., C.E.T., Data Collection and/or Processing: G.G., Z.M., C.E.T., B.M.U., Analysis and/or Interpretation: G.G., Literature Research: G.G., Critical Review: A.D.C., G.S., N.G., Writing: G.G., B.M.U.

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Case Report

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A Subacute Thyroiditis Case After SARS-CoV-2 Infection: A Case Report and Current Literature Review

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Abstract

Subacute thyroiditis (SAT), is a self-limiting inflammatory disorder which is linked to a viral infection. A few cases of SAT were reported after Severe Acute Respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection. We here reported a case of SAT that occurred two weeks after SARS-CoV-2 infection. A thirty-nine-year-old male with no comorbid diseases applied to our outpatient clinic with the complaints of sore throat, fatigue and subfebrile fever. He had a contact history of his wife who has a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test. The nasopharyngeal swab was performed and his SARS-CoV-2 RT-PCR test was confirmed positive. He recovered from all symptoms in one week. On the second week of the first diagnosis, he developed neck pain, fatigue, muscle pains, palpitation and tremors. Because his thyroid palpation was painful and he was more symptomatic thyroid function tests were performed. Thyrotropin was suppressed (0.01 mIU/L), free triiodothyronine and free thyroxine levels were high as 11 ng/L and 3.72 ng/dL, respectively. His cervical ultrasound also revealed SAT. He was treated with prednisolone, ibuprofen and propranolol. Within one week, there was a progressive resolution of signs and symptoms. After the third week, his laboratory results returned to normal ranges.

Keywords: Subacute thyroiditis, viral infection, COVID-19, endocrinology, antiviral treatment

Introduction

Subacute thyroiditis (SAT), which is also called de Quervain's thyroiditis is a self-limiting inflammatory disorder of the thyroid gland and a relatively rare cause of thyrotoxicosis generally linked to viral infection (1). It is the most common cause of anterior cervical pain (2). It is characterized by acute onset of neck pain, general symptoms and thyroid dysfunction mostly preceded by an upper respiratory infection which are caused by several viruses (1,3,4). A few cases of SAT after Severe Acute Respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection was reported in the literature (1,5-8). We here report a case of SAT which occurred two weeks after SARS-CoV-2 infection.

Case Report

A thirty-nine-year-old male with no medical history of concomitant disease applied to infectious diseases outpatient clinic with complaints of sore throat, fatigue and subfebrile fever. Chest X-ray was normal. Complete blood count, blood biochemistry and inflammatory markers were within normal ranges. He had a contact history with her wife who had a positive nasopharyngeal swab test for SARS-CoV-2 RNA. His SARS-CoV-2 reverse transcription polymerase chain reaction test was confirmed positive. Because he was symptomatic, favipiravir (with a loading dose of 800 mg bid, maintenance dose of 300 mg bid) was initialized according to national interim guideline (9). He recovered from all symptoms in one week. On the second week on the 28th of December, 2020 he developed pain, tenderness in the anterior cervical area, fatigue, muscle pains, palpitation and tremors. He was afebrile. On the physical examination palpation of the thyroid gland was painful and thyroid gland was enlarged, other systems were normal. Because he was more symptomatic and the thyroid gland was enlarged, complete blood count, blood chemistry, sedimentation, C-reactive protein (CRP) and thyroid function tests were performed. Serum markers of acute inflammation were positive (erythrocyte sedimentation rate, 79 mm/h; CRP, 74.9 mg/L), while

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white blood cell (10.6x10^9/L) and lymphocyte count (1.2 x 10^9/L) were within the normal ranges. Hepatic and renal function tests were within normal ranges. Thyrotropin (TSH) was suppressed (0.01 mIU/L), free triiodothyronine (fT3) and free thyroxine (fT4) levels were high as 11 ng/L and 3.72 ng/dL, respectively. TSH-receptor and anti-thyroglobulin antibodies were negative. His Coronavirus disease-2019 (COVID-19) IgM+IgG serology was positive. Viral hepatitis serology and anti-HIV tests were negative. Electrocardiogram demonstrated sinus tachycardia. His thyroid ultrasound was consistent with subacute thyroiditis. Prednisolone 16 mg/day, ibuprofen with a dose of 1200 mg/day and propranolol with a dose of 20 mg tid was initialized. Under this therapy, there was a progressive resolution of signs and symptoms. Within one week inflammatory markers became normal (Table 1). Prednisolone dosage reduced consecutively. In the third week, fT3 and fT4 levels started to reduce. In the fifth week, all thyroid tests were normalized and all of the symptoms were resolved and the treatment was stopped. Since this article is a case report, it does not contain any studies with animal or human participants performed by any of the authors. Informed consent has been obtained from the patient for publication of the case report.

Discussion

SAT was first defined in 1904 by DeQuervain. Viral infections are frequently addressed as a major cause of SAT and autoimmune thyroid diseases (3). Because most of the cases have been followed by upper respiratory tract infections or sore throats, viral infection was suggested as the main cause of SAT (3,4). It was associated with outbreaks of mumps, and the mumps virus has been cultured from the thyroid glands of included cases (10). The onset of the reported cases is often observed in summer (usually between June and September) and this seasonal distribution is similar to that of established some viral infections due to some Enteroviruses (such as Echovirus, Coxsackievirus A and B). It suggests that enteroviral infections might be responsible for most of the cases (11). Several viruses such as influenza, adenovirus, or less commonly Epstein-Barr and cytomegalovirus were also accused (1). SAT is often observed in women. It usually starts with sudden neck pain and is characterized by thyrotoxicosis in the beginning. Clinical symptoms have typical characteristics of viral infections including a prodromal episode with myalgia, fatigue and muscle pain (3). The thyroid gland is painful, tender and enlarged on palpation (6). Diagnosis of SAT is mainly based on clinical features, but also laboratory tests and imaging are also used (6).

The COVID-19 pandemic has started in late 2019 and rapidly has spread worldwide, with over 100 million people got infected, more than 2 million people have died because of this disease (12). COVID-19 can cause many chronic conditions in many organ systems. Thyroid dysfunction was reported in several cases (13,14). Also, a a few SAT cases were reported after SARS-CoV-2 infection (8,14). We here reported a case of SAT that occurred in a patient after SARS-CoV-2 infection. Although it is frequently observed in women in the literature, our patient was a thirty-nine-year-old male. The first symptoms of our case were neck pain, fatigue, muscle pain and the signs of thyrotoxicosis were observed, such as palpitation and tremors which were consistent with the previous literature (3,4,8). The natural clinical course of SAT includes an initial thyrotoxic phase followed by a hypothyroid phase with recovery to a euthyroid state (15). Our case was in a hyperthyroid state in admission, after three weeks his thyroid hormone levels started to reduce and on the fifth week he became euthyroid. The treatment choices include corticosteroids, non-steroid antiinflammatory drugs and beta-blockers if needed (15-17). Our patient had received prednisolone, ibuprofen and propranolol and symptoms started to resolve and in one week inflammatory markers became normal.

Table 1. Laboratory findings of patient

	Reference ranges	28.12.2020	05.01.2021	18.01.2021	05.02.2021
WBC (x10^9/L)	3.9-10.2	10.6	9.4	9.7	8.58
Lymphocyte count (x10^9/L)	1.1-4.5	1.2	1.6	3	2.97
CRP (mg/L)	0-5	74.9	5.35	0.5	0.5
Erytrocyte sedimentation rate (mm/h)	0-20	79	73	3	-
Free T3 (ng/L)	2.3-4.2	11	-	3.32	2.75
Free T4 (ng/dl)	0.89-1.76	3.72	-	2.12	0.98
TSH (mIU/L)	0.55-4.78	0.01	-	0	2.19
Anti TG (IU/mL)	<1.3	1	-	-	1
COVID-19 Ig M+IgG (index)	0-0.99	>10.00	-	-	-

WBC: White blood cell, CRP: C-reactive protein, TSH: Thyrotropin, COVID-19: Coronavirus disease-2019

The pathogenesis and etiology of SAT remain unclear. But the most common thought is that, this disease is due to a viral etiology or a post-viral inflammatory reaction which is observed in individuals with a genetic predisposition (6,18).

Conclusion

To date, a few cases of SAT have been reported during or after SARS-CoV-2 infection and we here reported a case of SAT which is probably associated with SARS-CoV-2 infection. Physicians should keep in mind that unusual clinical manifestations may be observed because of SARS-CoV-2 infection and they can occur during or after the infection.

Authorship Contributions

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