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Six-month follow-up outcomes of ICU and non-ICU COVID-19 patients: A cohort study

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Abstract:

BACKGROUND AND AIM: The long-term outcome of Coronavirus disease 2019 (COVID-19) patients discharged from the intensive care unit (ICU) is unclear. We investigated the effect of COVID-19 on lung structure, pulmonary function, exercise capacity, and quality of life in patients discharged from ICU and medical wards.

METHODS: A prospective single-center study was conducted on COVID-19 patients discharged from University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital between March 19 and September 1, 2020. Patients who were followed up for more than 48 h in ICU and more than 72 h in medical wards were included in the study. Computed tomography (CT) scores, pulmonary function tests, 6-min walking distance, and health-related quality of life were compared between ICU and medical ward patients 6 months after discharge.

RESULTS: A total of 70 patients were included in the final analyses, and 31 of them were discharged from ICU. ICU patients had higher CT scores than non-ICU patients at admission (17 vs 11) and follow-up visits (6 vs 0). Two-thirds of ICU patients had at least one abnormal finding on a follow-up CT. Advanced age (OR 1.08, 95% CI 1.02–1.15) and higher CT score at admission (OR 1.13, 95% CI 1.01–1.27) were risk factors for having radiological abnormalities on the follow-up CT. Of the patients discharged from ICU, 90% had at least one persistent symptom.

CONCLUSIONS: Many COVID-19 survivors, especially those with severe diseases, could not fully recover even after 6 months after their discharge from the hospital.

Keywords:

COVID-19, CT score, ICU patients, pulmonary function test, 6-min walking test

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has affected over 150 million people worldwide as of April 28, 2021.[1]

The onset symptoms of COVID-19 are fever, fatigue, shortness of breath, and dry cough.[2,3] Typically, chest tomography findings are peripheral, subpleural ground-glass opacities, bilaterally patchy shadows, and chest computed tomography (CT) findings are related to disease severity.[2,4,5] Although most cases were classified as mild, 14% of cases were severe and 5% of them were critical, requiring intensive care unit (ICU) admission.[6] Studies focus on pathogenesis, clinical manifestations, and complications during the early phase of the disease, but long-term outcomes still remain unclear.[7–9]

Some of the patients recovered completely, but some patients were unable to reach their former health status despite a long recovery period. Symptoms such as fatigue and dyspnea persist in half of the patients discharged from the hospital.[10,11] CT findings are reversible in most COVID-19 patients.[12] However, the data on the improvement of CT findings in ICU patients who have higher CT scores are lacking. Complete recovery may take a long time in mild and moderate cases as well as in severe patients who require ICU admission. More studies are needed on the long-term outcome in the post-COVID period, especially in ICU patients.[13]

The aim of this study was to evaluate the long-term effects of COVID-19 on lung structures, pulmonary functions, exercise capacity, and quality of life in discharged ICU patients and compare these findings with hospitalized non-ICU patients.

Materials and Methods

This is a single-center, prospective cohort study performed between January 15 and March 5, 2021, at University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital. This is a tertiary hospital specializing in pulmonary diseases and has been designated for patients with COVID-19 since March 2020. The study was approved by the local ethic committee (ethical approval number: 19-28.09.2020). Written informed consent was obtained from all participants. This study was registered on clinicaltrials.gov under the number NCT04715919. The study was carried out in acccordance with the Declaration of Helsinki 2013.

Patients

Patients who were followed up for more than 48 h in ICU and more than 72 h in medical wards due to COVID-19 between March 19 and September 1, 2020, were included in the study. We excluded the following patients: (1) those who have neurodegenerative diseases, (2) those who were readmitted to the hospital due to any other conditions, and (3) those with impaired movement due to physical disabilities. Patients were included in the study for at least 6 months after discharge from the hospital.

The diagnosis of COVID-19 was based on the interim guidance of the World Health Organization.[14] Antiviral treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was given according to the Turkish Ministry of Health COVID-19 Guidance.[15]

Procedures

Clinical data, including demographic characteristics (age, gender, and smoking status), antiviral treatment (hydroxychloroquine, favipiravir, convalescent plasma, and steroids), chest tomography results, and complication development during hospitalization were obtained from the hospital electronic record system. Patients were classified into two groups: ICU patients (followed in the ICU due to COVID-19) and non-ICU patients (hospitalized due to COVID-19 but followed in the pulmonary ward).

Patients were invited to the follow-up visit, by healthcare professionals, by telephone. All participants were consulted face to face by an investigator; asked to complete a questionnaire to assess their health status (Short Form-36, SF-36) and asked for persistent symptoms such as dyspnea, fatigue, and muscle weakness. A trained physiotherapist performed a 6-min walking test to assess functional exercise capacity. The pulmonary function test (PFT) was performed in the Pulmonary Functional Center according to American Thoracic Society and European Respiratory Society spirometry standardizations.[16]

Chest high-resolution computed tomography (HRCT) was performed at the end-inspiration in the supine position, 1.25 mm section thickness and 0.625 mm recon-

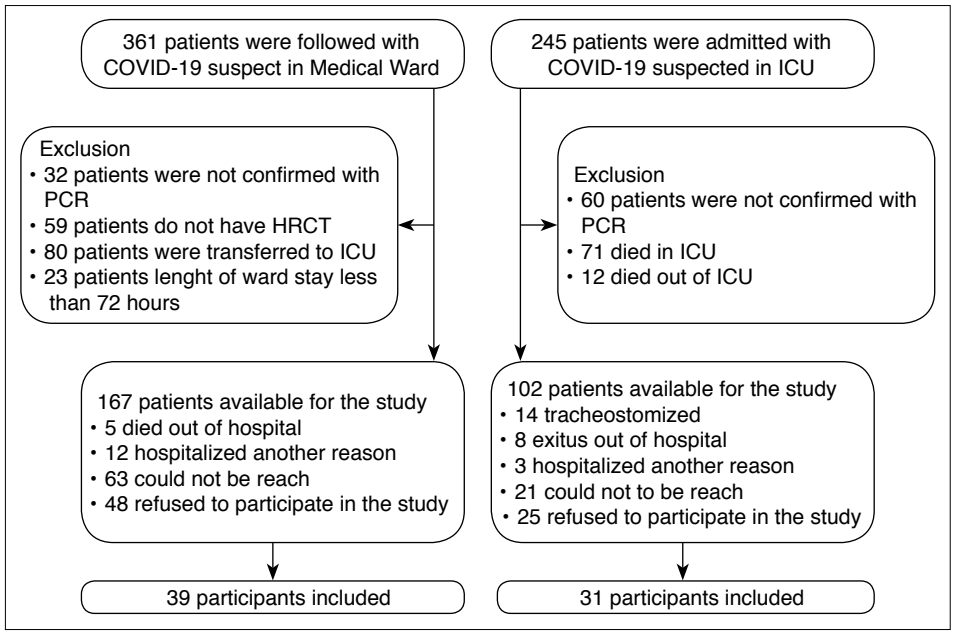

Figure 1: Flow chart of patients who admitted to the hospital with a suspect of COVID-19 between March 19 and September 1, 2020.

COVID-19: Coronavirus disease 2019, ICU: Intensive care unit, HRCT: High-resolution computed tomography, PCR: Polymerase chain reaction

struction with high resolution. An experienced radiologist cross-compared HRCT images during hospital stay and follow-up HRCT images. If a participant had more than one HRCT, final chest images were included in the comparison. Both lungs were divided into five lobes in accordance with normal anatomical structure. Each lung lobe was given a score according to the following criteria: 0, no involvement; 1, less than 5% involvement; 2, 5%–25% involvement; 3, 25%–50% involvement; 4, 50%–75% involvement; 5, more than 75% involvement. The total CT score was calculated semiquantitatively with the sum of the scores of the five lobes.[17]

The SF-36 test is a 36-item self-reported survey of quality of life. SF-36 contains eight categories that assess physical functioning, social functioning, role limitation due to physical and emotional problems, general and mental health, bodily pain, and vitality. Each category is scored from 0 (worst) to 100 (best) with higher scores showing better quality of life.[18] The translated and validated version of SF-36 was used for the study.[19]

The primary outcome was the percentage of patients with lung involvement in the 6-month follow-up CT scan.

Secondary outcomes were exercise capacity (distance of 6-min walking test), PFTs, and health state scores at the follow-up visit.

Statistical analysis

Continuous data were expressed as median (25^{th}–75^{th} percentiles), and categorical data were expressed as numbers (%). Normality was tested with the Kolmogorov–Smirnov test. Comparisons were performed using the Mann–Whitney U test for continuous variables when not normally disturbed and Fisher's exact test for categorical variables. A logistic regression model was used to estimate the odds ratio (OR) and 95% CI for risk factors for having radiological abnormality at a follow-up CT. According to a study performed on severe acute respiratory syndrome (SARS), 30% of patients showed abnormal radiological findings at the 6-month follow-up.[20] We also hypothesized that COVID-19 patients requiring ICU admission would have a twofold increase in lung involvement at the 6-month follow-up CT scan when compared with non-ICU patients. Assuming that 30% of non-ICU patients and 60% of ICU patients will have lung involvement in the 6-month follow-up CT, with a 5% type 1 error and 80% power, 40 patients in each group were needed for the analysis. A value of $p<0.05$ was considered significant. SPSS version 26 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

A total of 269 COVID-19 patients were discharged from our hospital between April 1 and September 1, 2020, and 70 patients were included in the study [Fig. 1]. The de-

Table 1: Demographic and clinical characteristics of the patients

Patient characteristics	ICU patients (n=31)		Non-ICU patients (n=39)		p
	n	%	n	%	
Age, years	59 (48–65)		56 (48–61)		0.40
Male gender	26	84	24	62	0.04
BMI, kg/m^2	31 (29–35)		30 (25–34)		0.20
Smoking status					
None	14	45	27	69	
Active smoker	0	0	2	5	
Former smoker	17	55	10	26	
Smoking time, years	30 (10–40)		15 (13–25)		0.25
Comorbidities					
COPD	5	16	2	5	0.13
Hypertension	16	52	12	31	0.07
DM	13	42	10	26	0.15
CAD	3	10	2	5	0.46
CHF	1	3	1	2	0.86
Malignancy	0	0	3	8	0.11
Charlson Comorbidity Index	1 (1–2)		1 (1–2)		0.16
Disease severity					
1-No O_2 therapy	0	0	18	46	<0.001
2-Only O_2 therapy	3	10	21	54	
3-NIV or HFNC	23	74	0	0	
4-IMV	5	16	0	0	
APACHE-2 score	11 (8–15)		–		
Treatment					
Hydroxychloroquine	21	68	33	85	0.09
Favipiravir	31	100	19	49	<0.001
Corticosteroid	26	83	3	8	<0.001
Convalescent plasma	12	39	0	0	<0.001
Tocilizumab	5	16	0	0	0.009
Antibiotics	31	100	37	95	0.2
Complications					
Acute renal failure	4	13	2	5	0.39
Hepatotoxicity	9	29	4	10	0.045
Sepsis	1	3	0	0	0.26
Length of hospital stay, days	19 (14–28)		8 (6–11)		<0.001
Length of ICU stay, days	9 (6–15)		–		
Time from symptoms to follow-up, days	209 (189–219)		190 (186–209)		0.016
Laboratory					
D-dimer, mg/L	1905 (995–3403)		673 (436–1025)		<0.001
Ferritin, ng/mL	1025 (495–1566)		321 (170–678)		0.001
Procalcitonin, ng/mL	0.24 (0.11–0.63)		0.08 (0.05–0.32)		0.17
CRP, mg/L	124 (56–226)		39 (11–91)		<0.001
LDH, U/L	326 (264–470)		248 (209–277)		0.004

Data are shown as n (%) and median (25th–75th percentiles). Data were compared using the Mann-Whitney U test or Fisher's exact test. ICU: Intensive care unit, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary arterial disease, CHF: Congestive heart failure, NIV: Noninvasive mechanical ventilation, HFNC: High Flow Nasal Cannula, IMV: Invasive mechanical ventilation, APACHE-2: Acute Physiology and Chronic Health Evaluation, CRP: C-reactive protein, LDH: Lactate dehydrogenase

mographic and clinical characteristics of the participants are shown in Table 1. The median age of the participants was 56 years, and 50 (71%) of them were males. The most common comorbid diseases were hypertension (40%) and diabetes mellitus (33%). Of the patients, 31 (44%) were admitted to the ICU, and the median length of ICU

Table 2: Chest CT scores and findings at admission and 6-month follow-up

CT findings	ICU patients (n=31)	Non-ICU patients (n=39)	p
CT score at admission, points	17 (11–24)	11 (10–15)	0.002
CT score at 6-month follow-up visit	6 (0–10)	0 (0–3)	0.001
Number of patients having at least one abnormal CT pattern at 6-month follow-up visit, n (%)	20 (65)	12 (31)	0.005

Data are shown as n (%) and median (25^{th}–75^{th} percentiles). Data were compared using the Mann-Whitney U test.
CT: Computed tomography; ICU: Intensive care unit

Table 3: Results of PFTs, 6MWD, and quality of life scores at the follow-up visit

Parameters	ICU patients (n=31)		Non-ICU patients (n=39)		p
	n	%	n	%	
FVC, % of predicted	85 (77–97)		95 (85–104)		0.73
FEV_1, % of predicted	95 (84–103)		99 (86–106)		0.18
FEV_1/FVC, % of predicted	112 (108–116)		109 (102–114)		0.94
PIF, % of predicted	96 (76–127)		100 (64–132)		0.98
PEF, % of predicted	90 (64–110)		79 (68–96)		0.42
6MWD, m	445 (346–515)		461 (390–527)		0.31
FVC <80% of predicted	9	31	5	14	0.09
FEV_1 <80% of predicted	6	21	7	19	0.9
FEV_1/FVC <80% of predicted	2	7	0	0	0.10
PIF <80% of predicted	8	28	12	33	0.61
PEF <80% of predicted	12	41	19	49	0.36
6MWD <80% of mean distance	13	42	11	28	0.22
SF-36 categories					
Physical functioning	80 (45–90)		80 (65–95)		0.48
Social functioning	50 (25–75)		63 (38–75)		0.23
Role limitation due to physical problems	50 (0–100)		50 (25–100)		0.16
Role limitation due to emotional problems	33 (0–100)		67 (0–100)		0.49
General health	65 (40–80)		60 (45–80)		0.79
Mental health	68 (48–84)		68 (52–76)		0.43
Bodily pain	88 (55–100)		90 (58–100)		0.81
Vitality	65 (40–80)		60 (45–80)		0.68

Data are shown as n (%) and median (25^{th}–75^{th} percentiles). Data were compared using the Mann-Whitney U test.
PFT: Pulmonary function test, 6MWD: 6-Minute walking distance, ICU: Intensive care unit, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s; PIF: Peak inspiratory flow, PEF: Peak expiratory flow, SF-36: Short Form-36

stay was 9 days. The median length of hospital stay was 12 days, and the time from the onset of symptoms to the follow-up visit was 198 days.

ICU patients had a higher median CT score at admission than non-ICU patients [17 (IQR 11–24) vs 11 (IQR 10–15), p=0.002]. CT scores at the follow-up visit remained higher in ICU patients [6 (0–10) vs 0 (0–3), p=0.001]. Twenty ICU patients (65%) and 12 non-ICU patients (31%) had at least one CT finding in the follow-up CT (p=0.005) (Table 2). The most common CT finding was ground glass opacity (GGO) in the follow-up CT, followed by subpleural lines and irregular lines. When the presence of ICU admission, age, gender, and CT score at admission was introduced into a logistic regression model, age (OR 1.08, 95% CI 1.02–1.15) and higher CT score at admission (OR 1.13, 95% CI 1.01–1.27) were independent risk factors for having radiological abnormality at a follow-up CT.

Of the participants, 79% had at least one persistent symptom. Individuals discharged from the ICU had a higher percentage of persistent symptoms (90% vs 67%, p=0.033). Effort dyspnea was the most common persistent symptom, followed by fatigue and muscle weakness. Women had a higher percentage of persistent symptoms than men.

Table 4: Association between CT scores and PFT impairment

	FVC <80% of predicted (n=14)	FVC ≥80% of predicted (n=51)	p
CT scores at admission	11 (9–20)	14 (10–17)	0.78
CT scores at 6-month follow-up	7 (4–10)	0 (0–4)	0.007
	FEV_1 <80% of predicted (n=13)	FEV_1 ≥80% of predicted (n=52)	
CT scores at admission	10 (10–11)	15 (11–18)	0.11
CT scores at 6-month follow-up	5 (0–10)	0 (0–5)	0.036
	PIF <80% of predicted (n=20)	PIF ≥80% of predicted (n=45)	
CT scores at admission	11 (10–14)	15 (11–18)	0.07
CT scores at 6-month follow-up	3 (0–7)	0 (0–9)	0.55
	PEF <80% of predicted (n=31)	PEF ≥80% of predicted (n=34)	
CT scores at admission	11 (8–15)	15 (12–19)	0.006
CT scores at 6-month follow-up	2 (0–6)	0 (0–8)	0.19

Data are shown as median (25^{th}–75^{th} percentiles). Data were compared using the Mann-Whitney U test. CT: Computed tomography, PFT: Pulmonary function test, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, PIF: Peak inspiratory flow, PEF: Peak expiratory flow

Table 5: Assessment of quality of life by gender

SF-36 categories	Male (n=50)	Female (n=20)	p
Physical functioning	85 (75–90)	58 (45–75)	<0.001
Social functioning	63 (37–87)	50 (31–69)	0.17
Role limitation due to physical problems	75 (25–100)	0 (0–50)	0.002
Role limitation due to emotional problems	67 (30–100)	17 (0–67)	0.011
General health	70 (50–85)	45 (38–63)	0.004
Mental health	70 (56–76)	58 (40–68)	0.026
Bodily pain	90 (78–100)	59 (45–83)	<0.001
Vitality	45 (25–58)	70 (50–85)	0.002

Data are shown as median (25^{th}–75^{th} percentiles). Data were compared using the Mann-Whitney U test. SF-36: Short Form-36

A total of 65 participants (93%) completed the PFT, and 5 participants were unable to complete the test. The results of PFT are summarized in Table 3. Forced vital capacity, peak expiratory flow (PEF), and peak inspiratory flow (PIF) were the most affected parameters in ICU patients. PEF and PIF were the two most affected parameters in non-ICU patients. Higher CT scores at follow-up visits were found to be associated with impairment of PFT (Table 4).

The median distance of 6-min walking tests was similar in both groups; 445 m in ICU patients and 461 m in non-ICU patients. Thirteen participants (42%) in the ICU group and 11 participants (28%) in the non-ICU group were below 80% of the expected walking distance by age and weight.

Assessment of quality of life by SF-36 was similar in the two groups. Social functioning and role limitation due to physical and emotional problems were the most affected SF-36 categories (Table 3). The quality-of-life scores were lower in female participants than in male participants (Table 5).

Discussion

The main finding of this study was that the CT findings and symptoms (especially effort dyspnea, fatigue, and muscle weakness) may not be totally resolved 6 months after the onset of symptoms in patients who require ICU admission. Also, some of these patients may encounter impaired PFTs and decreased exercise capacity. Impairment of quality of life was comparable between ICU and non-ICU patients.

Chest CT has been frequently used as a diagnostic tool during the COVID-19 outbreak, and CT severity scores were related to disease severity.[21] In our study, patients who were admitted to ICU had higher CT scores than patients admitted to the medical ward, and this result was consistent with previous studies.[21,22] At the follow-up visit, patients who were discharged from ICU had higher CT scores than patients who were discharged from the medical ward (6 vs 0). CT findings were totally resolved in most non-ICU patients, but most ICU patients had abnormal CT findings at the follow-up visit. In a previous study, most of the CT findings were resolved in non-severe COVID-19 patients within 4 weeks after discharge.[12,23] However, as the severity of the disease increases, the recovery time may be longer. In a large cohort, patients with increased disease severity had higher CT scores at follow-up visits.[24] We found two-thirds of ICU patients had at least one of the CT findings at follow-up visits: irregular lines, subpleural lines, and GGO were the most common patterns in chest CT. We also found advanced age and higher CT scores at admission were risk factors for having abnormal CT findings at the follow-up visit. Disease severity was found to be an independent risk factor for the percentage change in CT score in the previous study.[24] Positive pressure ventilation or higher levels of fraction of inspired oxygen (FiO_2), which are frequently used in serious patients, may themselves cause lung damage and may inhibit complete recovery.[25–27]

We found PFT impairment was more frequent in individuals who were discharged from ICU even though the results were not statistically significant. Patients with severe disease were more prone to PFT impairment in the early convalescence phase and long term.[23,24] Patients with PFT impairment had higher CT scores at the follow-up visit (Table 4). It is difficult to associate changes in PFTs with COVID-19 because a few patients had respiratory diseases, and most of the patients had not had a PFT before. Nevertheless, patients with impaired PFT had higher scores at the follow-up CT, suggesting a relationship between partial improvement in CT findings and PFT impairment.

The median distance of 6-min walk was similar in both the patients discharged from ICU and from the medical ward, and these results are consistent with a previous study.[24] However, the 6-min walking test was found to be less than 80% of the expected value in half of the patients discharged from the ICU. Immobilization, severity of illness, and use of corticosteroids are risk factors for reduced exercise capacity.[28] ICU patients had these risk factors; thus, reduced exercise capacity could be expected in these patients. Prolonged immobilization after hospital discharge and restrictions to prevent transmission, such as a general curfew, may have limited the mobilization of these patients in the recovery phase.

We found that 79% of the participants had at least one persistent symptom, and patients with severe disease had a higher percentage of persistent symptoms. The percentage of residual symptoms in COVID-19 varies from 49% to 79% in previous studies.[10,24] Effort dyspnea, fatigue, and muscle weakness were the most common persistent symptoms in our and a previous study.[24]

Impairment of quality of life was observed in SF-36 categories, especially social functioning and role limitation due to physical and emotional problems. Impairment of quality of life was similar in both ICU and non-ICU patients. This result is consistent with long-term follow-up in SARS patients.[20] The percentage of residual symptoms and impairment of health status were significantly higher in female participants. Female survivors were more prone to depression and anxiety after the previous SARS outbreak.[29] The severity of the disease and the female gender were found to be risk factors for persistent psychological symptoms,[24] not only disease-related causes but also social restrictions (such as quarantine and curfew to prevent the spread of the disease), increased stress, anxiety, and depression in females.[30] Psychological distress, anxiety, and depression may aggravate persistent symptoms and influence the impairment of quality of life.

This study has several limitations. This is a single-center study, so these results cannot be generalized to other centers. Although the desired number of patients could not be reached in the ICU patient group, the study has sufficient power (0.83) to test the difference between the two groups for the primary outcome. A few patients who were followed up with invasive mechanical ventilation (IMV) could be included in the study due to the higher mortality and morbidity in patients who received IMV. Therefore, the long-term outcome of mechanically ventilated patients remain unclear. We could not measure the diffusion of carbon monoxide, which is frequently impaired in patients with SARS or COVID-19, due to technical issues in our pulmonary functional center. Most of the patients did not have PFT before, and 6-min walking

distance was unknown. Therefore, we cannot directly associate COVID-19 and PFT or 6-min walking impairment. The fact that most of the participants were men may have affected the results, especially the assessment of the quality of life.

Conclusion

This study is one of the first studies comparing the long-term outcome of patients with COVID-19 who were admitted to ICU and medical wards. A number of COVID-19 survivors could not fully recover within 6 months of hospital discharge. Unresolved CT findings, impaired PFT, and decreased exercise capacity might be persistent in ICU patients even after 6 months. COVID-19 survivors, especially those with severe diseases, may have persistent lung injuries; therefore, they should be followed up for a long time.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital Ethics Committee (No: 19, Date: 28/09/2020).

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Peer-review
Externally peer-reviewed.

Authorship Contributions
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