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Original Article

Evaluation of Long-Coronavirus Disease 2019 Cases Readmitted to Intensive Care Units Due to Acute Respiratory Failure: Point Prevalence Study

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Abstract

OBJECTIVE: Coronavirus disease 2019 (COVID-19) caused morbidity and mortality worldwide. Besides the acute effects, subacute and long-term effects are defined as long-COVID causing morbidity. The intensive care unit (ICU) data of long-COVID-19 cases were evaluated with the participation of 11 centers.

MATERIAL AND METHODS: Study was designed by Turkish Thoracic Society Respiratory Failure and Intensive Care Working Group to evaluate long COVID-19 patients. All patients followed up in the ICU with long-COVID diagnosis were included in point prevelance study.

RESULTS: A total of 41 long COVID-19 patients from 11 centers were included in the study. Half of the patients were male, mean age was 66 ± 14, body mass index was 27 ± 5. Hypertension, diabetes mellitus, lung cancer, malignancy, and heart failure rates were 27%, 51%, 34%, 34%, and 27%, respectively. Eighty percent had received COVID vaccine. Patients had moderate hypoxemic respiratory failure. APACHE II, SOFA score was 18 (14-26), 6 (3-8), respectively. Forty-six percent received invasive mechanical ventilator support, 42% were sepsis, 17% were septic shock. Bilateral (67%), interstitial involvement (37%) were most common in chest x-ray. Fibrosis (27%) was detected in thorax tomography. Seventy-one percent of patients received antibiotherapy (42% carbapenem, 22% linezolid). Sixty-one percent of the patients received corticosteroid treatment.

CONCLUSION: More than half of the patients had pneumonia and the majority of them used broad-spectrum antibiotics. Presence of comorbidities and malignancies, intensive care severity scores, intubation, and sepsis rates were high. Receiving corticosteroid treatment and extensive bilateral radiologic involvement due to COVID-19 might be the reasons for the high re-admission rate for the ICUs.

KEYWORDS: Post-acute COVID-19 syndrome, intensive care, respiratory failure, acute respiratory distress syndrome, hospital-acquired pneumonia, steroids

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INTRODUCTION

Nowadays, unlike other viruses transmitted by the respiratory route, the long-term effects of the coronavirus diease 2019 (COVID-19) virus, which can harm numerous organ systems and is categorized as long COVID, are emerging as a significant public health problem.[1]

Long-COVID syndrome is defined as the existence of cardiovascular, gastrointestinal, hematological, neuropsychiatric, and physical symptoms, affecting different organ systems that persist more than 4-12 weeks in a patient with a history of COVID-19, and cannot be explained by any other cause.[2-4]

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Although the risk factors for the development of long-COVID syndrome are unknown, studies have been conducted to determine which organ systems are affected and how they are affected. Furthermore, there are research on the morbidity, quality of life, and outpatient follow-up results of long-COVID-19 cases in the current literature.[5-7]

Since long-COVID syndrome has been researched in patients who were followed up on and discharged from the intensive care unit (ICU) due to serious COVID-19 infection, no adequate research on re-hospitalization of long-COVID patients in the ICU has been conducted.[8]

We aimed to evaluate the intensive care outcomes of long-COVID patients during re-admission to the ICU due to acute respiratory failure.

MATERIAL AND METHODS

Multicentered, cross-sectional, 1-day point prevalence study. Current studys' announcement was performed by e-mail through the Turkish Thoracic Society among the members currently practicing in the ICUs. Afterwards, the consent forms were shared with the centers. All ongoing symptomatic COVID-19 cases categorized in long-COVID admitted to the ICU between December 15, 2021, 08:00 AM, and December 16, 2021, 08:00 AM, were included in the study. All data from centers were obtained via e-mail. The study was approved by the University of Health Sciences İzmir Dr Suat Seren Chest Diseases and Surgery Training Hospital Ethical committee, 2020-KAEK-139, according to the Declaration of Helsinki.

Ongoing symptomatic COVID-19 patients who were discharged after being hospitalized due to severe COVID pneumonia and then admitted to the ICU for acute respiratory failure at 4-12 weeks were included in the study.

Patients definition for long-COVID-19 was provided from National Institute for Health and Care Excellence guidelines on Long-COVID. In the current study, ongoing symptomatic COVID-19 was defined as signs and symptoms developing during/after the COVID-19 infection persisting more than 4-12 weeks and also cannot be explained by any other diagnosis.

Accordingly, long-COVID consists of 2 categories as below:

- Ongoing symptomatic COVID-19, the symptoms lasting for 4-12 weeks
- Post-COVID-19 syndrome, with symptom persistence beyond 12 weeks[9]

Inclusion Criteria

- Ongoing symptomatic COVID-19 patients, previously diagnosed COVID-19 and/or thorax computed tomography (CT)

Exclusion Criteria

- Patients refused to participate in the study
- Age <18 years
- Pregnancy

Assessments

Demographic features (age, gender), smoking history, vaccination status, ICU diagnosis, comorbidities, ICU duration time, radiologic features (chest x-ray, thorax CT if available), Acute physiology health evaluation II score (APACHE II), and the Sequential Organ Failure Assessment (SOFA) scores, type of respiratory support which patients received (nasal oxygen, mask oxygen, high flow oxygen, noninvasive mechanical ventilation [NIV], IMV), presence of sepsis, septic shock, multi-organ failure, adult respiratory distress syndrome, and types of medical treatment (antibiotics, corticosteroids, anticytokine, etc.) were recorded for analysis.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences, Statistics for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive analysis was performed for patients' demographics and clinical data. For non-parametric continuous variables, the median with interquartile range was used, and for parametric continuous variables, the mean ± standard deviation (SD). Counts and percentages were used when applicable.

RESULTS

A total of 41 patients from 11 centers were included in the current study. Table 1 summarizes the demographic features, ICU admission place, comorbidities of the ongoing symptomatic COVID-19 cases at the study day. Approximately half of the cases were male, and the mean age was 66 ± 14 years. Nearly half of the cases were current smokers. The most frequent comorbidities were malignancy and diabetes mellitus, 60%, 34%, respectively. Besides, 81% of the patients had comorbidities. The COVID-19 vaccination rate was 80%.

The ICU data, treatments, type of respiratory support, length of stay, intubation/extubation duration, type of respiratory support (nasal oxygen, mask oxygen, high flow oxygen, NIV, IMV), types of medical treatment, and discharge place, were shown in Table 2. The most frequent diagnosis in ICU admission was pneumonia 28 (68%). Nearly half of the patients

Main Points

- Long-coronavirus disease (COVID) syndrome is defined as the existence of cardiovascular, gastrointestinal, hematological, neuropsychiatric, and physical symptoms, affecting different organ systems in patients with a history of COVID-19, and cannot be explained by any other cause**.**
- Long COVID consists of 2 categories as below: acute COVID-19, with symptoms lasting for 4-12 weeks, and post-COVID-19 syndrome, with symptom persistence beyond 12 weeks.
- In the present study, we aimed to evaluate the intensive care outcomes of long COVID patients during re-admission to the ICU due to acute respiratory failure.
- Ongoing symptomatic COVID-19, especially accompanying comorbidity and malignancy might have increased intensive care unit re-admission. In addition, the risk of pneumonia and need for broad-spectrum antibiotics might be increased in the group of patients receiving steroid treatment due to the sequelae of COVID-19.

Table 1. Demographic Characteristics of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Male, n (%)	21 (51)
Age, mean ± SD	66 ± 14
BMI, mean ± SD	27 ± 5
Smoking status, n (%)	
Current smoker	22 (54)
Ex-smoker	6 (15)
Non-smoker	12 (31)
Intensive care unit admission place, n (%)	
Emergency unit	14 (34)
Ward	17 (42)
Outer center ICU	7 (17)
Outer center emergency unit	3 (7)
Comorbidities, n (%)	33 (81)
Congestive heart failure	11 (27)
Hypertension	21 (51)
Diabetes mellitus	14 (34)
Coronary artery diseases	7 (17)
Chronic kidney failure	6 (15)
Alzheimer's disease	4 (10)
Parkinson disease	2 (5)
Cerebrovascular event	5 (12)
Sequelae of tuberculosis	1 (2)
Extra-pulmonary malignancy	11 (27)
Pulmonary malignancy	14 (34)
COVID vaccination, n (%)	33 (80)

BMI, body mass index; COVID, coronavirus disease 2019; ICU, intensive care unit.

Table 2. Intensive Care Data of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to the Intensive Care Units Due to Acute Respiratory Failure

ICU Diagnosis, n (%)	
COPD exacerbation	6 (15)
Pneumonia	28 (68)
Pulmonary embolism	1 (2)
Pneumothorax	1 (2)
Pulmonary edema	6 (15)
Interstitial lung disease exacerbation	4 (10)
Acute kidney failure	4 (10)
Cerebrovascular event	4 (10)
ICU Data	
P/F ratio, median (IQR)	170 (110-260)
APACHE II, median (IQR)	18 (14-26)
SOFA, median (IQR)	6 (3-8)
ARDS, n (%)	4 (10)
Sepsis, n (%)	17 (42)
Septic shock, n (%)	7 (17)
Multi organ failure, n (%)	3 (7)
Intubation, n (%)	23 (56)
Tracheostomy, n (%)	4 (10)
Extubation, n (%)	5 (12)
Type of Respiratory Support, n (%)	
Invasive mechanical ventilation	19 (46)
Non-invasive mechanical ventilation	6 (15)
Nasal oxygen	6 (15)
Mask oxygen	2 (5)
Reservoir mask oxygen	3 (7)
High flow nasal cannula oxygen	3 (7)
Intubation day, median (IQR)	9 (1-16)
Extubation day, median (IQR)	2 (1-4)
ICU length of stay, median (IQR)	10 (6-18)
Discharge site from ICU, n (%)	4 (10)
Home, n (%)	1 (2)
Ward, n (%)	3 (7)
Type of Respiratory Support After Discharge, n (%)	
LTOT	4 (10)
CPAP	1 (2)
BIPAP-ST	2 (5)
HomeVENT	2 (5)

APACHEII, acute physiology health evaluation II score; ARDS, acute respiratory distress syndrome; BIPAP-ST, bilevel positive airway pressure spontaneous/timed; CPAP, continuous positive airway pressure; ICU, intensive care unit; IQR, interquartile range; LTOT, long-term oxygen therapy; P/F ratio, partial arterial oxygen pressure to fractional inspired oxygen; SOFA, Sequential Organ Failure Assessment.

had sepsis. The APACHE II score and partial arterial oxygen pressure to fractional inspired oxygen (P/F) ratio was 18 (14-26), 170 (110-260), respectively. Intubation rate was observed to be 56% and 46% of required mechanical ventilation support. Long-term oxygen therapy was prescribed for 10% of the patients at discharge.

Table 3 summarizes the medical treatment of ongoing symptomatic COVID-19 patients. Among the study population 61% of the patients received corticosteroid, and 71% of the patients used antibiotherapy. Most frequent reason for receiving antibiotic treatment was hospital acquired pneumonia (32%). The most commonly administered antibiotics were meropenem and linezolid 42%, 22%, respectively.

Interstitial involvement was detected in 37% of patients on chest radigraphy whereas fibrosis and consolidation/ground glass involvement were detected via computerized thorax tomography, 27% respectively (Table 4).

DISCUSSION

In our study, more than half of the ongoing symptomatic COVID-19 patients were hospitalized in the ICU due to

Table 3. Medical Intensive Care Treatments of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Corticosteroid, n (%)	25 (61)
Methylprednisolone	16 (39)
Prednisolone	2 (5)
Dexamethasone	6 (15)
Hydrocortisone	1 (2)
Antibiotherapy, n (%)	29 (71)
Antibiotherapy day, mean ± SD	1.8 ± 0.5
Antibiotherapy reason, n (%)	
CAP	11 (27)
HAP	13 (32)
VIP	4 (10)
UTI	3 (7)
Catheter infection, n (%)	1 (2)
Wound infection, n (%)	2 (5)
Antibiotics, n (%)	
Meropenem, n (%)	17 (42)
Teicoplanin, n (%)	3 (7)
Linezolid, n (%)	9 (22)
Coly-Mycin, n (%)	5 (12)
Fluconazole, n (%)	4 (10)
Amphotericin B, n (%)	2 (5)
Daptomycin, n (%)	2 (5)
Levofloxacin, n (%)	4 (10)
Tigecycline, n (%)	4 (10)
Ertapenem, n (%)	2 (5)
Piperacillin–tazobactam, n (%)	3 (7)
Moxifloxacin, n (%)	2 (5)
Vancomycin, n (%)	2 (5)
Posacanazole, n (%)	1 (2)
Trimethoprim–sulfamethoxazole, n (%)	1 (2)
Fosfomycin, n (%)	1 (2)
Ceftazidime, n (%)	3 (7)
Amikacin, n (%)	1 (2)
Ceftazidim-avibactam, n (%)	1 (2)

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; UTI, urinary tract infection; VIP, ventilatory acquired pneumonia.

pneumonia and the majority of them used broad-spectrum antibiotics. In addition, the rates of comorbidities and malignancies were found to be high. Besides, intensive care severity scores (APACHE II; SOFA), intubation, and sepsis rates were high, and P/F rates were low. In the present study, it has been shown that more than half of the patients who were discharged and re-admitted to the ICU after suffering from COVID-19 had received corticosteroid therapy and had bilateral involvement due to COVID-19 on a chest x-ray. The use of steroids, lung involvement/fibrosis might be among the reasons for the severity of critical illness in ICU.

Table 4. Radiologic Features of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Chest X Ray	
Normal, n (%)	5 (12)
Lobar involvement. n (%)	4 (10)
Lobular involvement, n (%)	4 (10)
Diffuse involvement, n (%),	5 (12)
İnterstitial involvement, n (%)	15 (37)
Localization, n (%)	
Right	6 (15)
Left	3 (7)
Bilateral	27 (67)
Computerized thorax tomography, n (%)	
Ground glass opacity, n (%)	7 (17)
Consolidation, n (%)	2 (5)
Consalidation and ground glass opacity, n (%)	11 (27)
Fibrosis, n (%)	11 (27)
Lung opacity, n (%)	3 (7)

Recent studies revealed that the ratio of long COVID symptoms was higher in females. Factors predicting long COVID were age over 70 years, to have >5 symptoms during the presence of comorbidities, and female gender.[10-12] In the present study, gender ratios were similar, and 81% of the ongoing symptomatic COVID patients had comorbidities. Additionally, a few studies reported that males were as likely to develop long-COVID as females.[13,14]

In our study, the most frequent comorbidities were malignancy and DM among the ongoing symptomatic COVID patients admitted to the ICU. Lee et al[15] reported that 28% of the cancer patients with COVID-19 died, and mortality was associated with old age, male gender, existing comorbidities such as hypertension and cardiovascular disease. On the other hand, it was determined that the type of oncologic treatment (cytotoxic chemotherapy, immunotherapy, hormonal therapy, etc.) had no effect on mortality. In the current study, treatments of patients with malignancy were not evaluated.

Coronavirus disease-ICU group on behalf of the REVA network and the COVID-ICU investigators evaluated the risk factors of 90-day mortality during post-ICU admission among 4244 patients who survived from COVID-19. Ventilator-associated pneumonia was diagnosed in nearly half (58%) of these patients and on day 90, 1/3 of patients had died. Independent predictors of 90-day mortality were older age, immunosuppression, severe obesity, DM, higher renal and cardiovascular SOFA score components, and a lower PaO_2/FiO_2[16] ratio. In the current study, ongoing symptomatic COVID patients were admitted to the ICU mostly with the diagnosis of pneumonia (68%) and nearly half of the patients had sepsis. The APACHE II scores were high and P/F ratio was low. Half of the patients had received intubation and required mechanical ventilation support.

Ruiz-Bastiá and coworkers evaluated a total of 1251 respiratory samples from 1195 critically ill COVID-19 patients and reported that all patients received broad-spectrum antibiotherapy as an empirical treatment, and the isolated bacteria were mainly Enterobacterales followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[17] In our study, 2/3 of the patients received broad-spectrum antibiotherapy, most frequently administered antibiotics were meropenem and linezolid.

Various studies consider smoking status, male gender as a risk factor for post-COVID-19 pulmonary fibrosis (PCPF).[18-20] On the contrary, in a meta-analysis male gender, smoking status, and body mass index were not found to be significant risk factors for the development of PCPF; only COPD was reported as a risk factor.[21] In a study performed on 55 COVID-19 survivors 3 months after recovery, radiological abnormalities (ground-glass opacity, consolidation, and interstitial thickening) persisted in 70% of the patients.[22] In the present study, 1/3 of the post-COVID-19 patients admitted to the ICU had fibrosis on computerized thorax tomography. Since the current study was designed as cross-sectional, previous computerized thorax tomography records were not obtained, and other factors that might cause lung fibrosis could not be investigated. Additionally, in the current study, 11% of the study population had fibrosis detected in computerized thorax tomography.

The main limitation of our study is the short time period of the study, since the study designed as a cross-sectional 1-day point prevalence study, results only reflect the study day. Follow-up results, ICU outcomes, factors affecting mortality, could not be provided. Since the study was conducted as multi-centered, data was obtained from different ICUs with various protocols which could cause heterogeneity. However, the evaluation of 11 centers could provide important data about ongoing symptomatic COVID-19 patients' ICU data.

In conclusion, among ongoing symptomatic COVID-19 cases, especially accompanying comorbidity and malignancy, ICU re-admission rate was high. In order to reveal the association between the ICU readmission and presence of comorbidity, malignancy risk analysis should be performed with a control group. In addition, the risk of pneumonia and need for broad-spectrum antibiotics might be increased in the group of patients receiving steroid treatment due to the sequelae of COVID-19. In daily clinical practice, the number of Post-COVID cases that would be increased as time passes should be followed up more closely and multidisciplinary in the ICU.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences İzmir Dr Suat Seren Chest Diseases and Surgery Training Hospital (Approval No: 2020-KAEK-139, date: November 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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