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Evaluation of patients with negative PCR tests after COVID-19 pneumonia in intermediate-level intensive care unit

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ABSTRACT

Objectives: The need for an intensive care unit has increased during the pandemic of coronavirus disease (COVID-19). For this reason, intermediate-level intensive care units (IICUs) were established in hospitals worldwide. This study aims to evaluate the data of patients that hospitalized in IICU.

Methods: Patients under treatment for COVID-19 were followed up in IICU after the negative polymerized chain reaction test. A total of 52 patients were evaluated retrospectively between August 24, 2020 and March 1, 2021. The patients were divided into two groups according to discharge status from IICU (Group 1: exitus, Group 2: transferred to clinic, or discharged home). Demographic data, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II), Glasgow Coma Scale (GCS), treatments and procedures, and complications were recorded.

Results: Seventeen (32.7%) of 52 patients who were followed up in IICU died. Thirty-five patients (67.3%) were transferred to the clinic or discharged home. The APACHE II scores at admission to IICU were higher in Group 1 (26.11 ± 5.86) than in Group 2 (23.43 ± 6.32) but not statistically significant. GCS was statistically significantly lower in Group 1 than in Group 2 (7.82 ± 2.42 and 10.25 ± 2.58, respectively, $p = 0.002$). Mechanical ventilation rate (82.3%) and the need for inotropic agents (76.5%) were higher in Group 1 ($p = 0,034$ and $p < 0.001$, respectively). Tracheostomy was applied to 5 of all patients, and percutaneous endoscopic gastrostomy was performed 4 of them.

Conclusions: We think that IICU created during the pandemic provides effective treatment for patients needing intensive care. We think IICU is beneficial in providing quick patient discharge in tertiary intensive care units.

Keywords: COVID-19, pneumonia, intensive care unit, intermediate, physiotherapy, mortality

In December 2019, acute respiratory distress syndrome (ARDS) caused by the SARS- CoV-2 virus in Wuhan, China, was defined as the new type of coronavirus disease, COVID-19 [1]. COVID-19 disease was reported as a pandemic by the World Health Organization (WHO) on March 2020, when the first case was seen in Turkey [2]. Due to the high virulence of COVID-19 disease, its rapid spread, and the lack of an effective treatment or vaccine, respiratory distress in patients has spread rapidly. These circumstances in-

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creased the need for ICU treatment. Hospitals all over the world changed their infrastructure and organization. Cooperation between different disciplines and new strategies were designed to manage the pandemic. New ICUs quickly entered service. IICUs reduced the overload of intensive care units during the current COVID-19 pandemic. Development, reorganization, and optimization of IICUs were achieved [3].

Patients with severe COVID-19 pneumonia receive ARDS treatment, viral infection treatment, and respiratory support treatment in the tertiary level ICU [4]. The duration of treatment is prolonged due to the presence of additional comorbidities and the development of complications. Intermediate intensive care units are needed for patients whose COVİD-19 PCR test is negative after treatment and who need intensive care follow-up. It is essential to determine the conditions encountered during the follow-up and treatment of these patients and the complications that develop after the disease.

This study aims to evaluate the clinical features and outcomes of patients who have negative PCR tests after treatment for COVID-19 pneumonia, continue to need ICU, and are hospitalized in the IICU.

METHODS

Ethics committee approval of the study was obtained from Bursa Yüksek İhtisas Training and Research Hospital with protocol number 2011-KAEK-25 2021/03-26. Between August 24, 2020 and March 1, 2021, 52 patients who were negative for the COVID-19 PCR test twice and followed up in the IICU were evaluated. Patients under 18 years old and who did not have COVID-19 pneumonia were excluded from the study. The patients were divided into two groups according to their exit from the IICU. Patients who died were classified as Group 1, and patients who were transferred to the clinic or discharged home were classified as Group 2. Demographic data, APACHE II scores and GCS, length of stay, type of respiratory support (mask/nasal oxygen, noninvasive ventilation, and high flow oxygen, mechanical ventilator), surgical procedures (tracheostomy and percutaneous endoscopic gastrostomy(PEG)), inotropic/vasoactive treatment, nutrition type, physical therapy, presence of pressure ulcers, and complications were recorded retrospectively from patient files and the hospital automation system.

Statistical Analysis

Data analysis was accomplished by IBM SPSS 23.0 statistical program. Descriptive statistics were specified as frequencies and percentages for qualitative data. Quantitative data were expressed as mean and standard deviation. The normal distribution was evaluated with the Kolmogorov-Smirnow test. In addition, Fisher's exact test was used for categorical variables, Mann Whitney U test was utilized for analysis of quantitative data. The statistical significance level was accepted as $p < 0.05$.

RESULTS

Seventeen (32.7%) of 52 patients who were followed

Table 1. Demographic data and comorbidities of patients

Parameters	All patients (n = 52)
Age (year)	70.55±11.40
Male, n (%)	22 (42.3)
Female, n (%)	30 (57.7)
BMI (kg/m^2)	28.55 ± 3.48
APACHE 2	24.32 ± 5.94
GCS	9.46 ± 2.76
Comorbidities, n (%)	
DM, COPD, CVD, HT	11 (21.2)
CAD, HT	10 (19.2)
CRF, ARF	5 (9.6)
DM	9 (17.3)
CVD	9 (17.3)
COPD	4 (7.7)
Malignancy	3 (5.8)
Substance Abuse	1 (1.9)

Data are shown as mean ± standard deviation or n (%). BMI = Body Mass Index, APACHE = Acute Physiology and Chronic Health Evaluation, GCS = Glasgow Coma Scale, DM = Diabetes mellitus, COPD = Chronic Obstructive Pulmonary Disease, CVD = Cerebrovascular Disease, CAD = Coronary Artery Disease, HT = Hypertension, CRF = Chronic Renal Failure, ARF = Acute Renal Failure

Table 2. Age, APACHE II and GCS scores of the groups, length of stay in Covid and intermediate ICUs

Parameters	Group 1 (n = 17)	Group 2 (n = 35)	*p* value
Age (year)	71.25 ± 9.71	69.11 ± 14.3	0.830
APACHE II	26.11 ± 5.86	23.43 ± 6.32	0.318
GCS	7.82 ± 2.42	10.25 ± 2.58	**0.002**
Length of stay in Covid ICU (day)	17.41 ± 25.27	15.60 ± 16.18	0.717
Length of stay in IICU (day)	14.64 ± 13.92	20.91 ± 17.33	0.133

Data are shown as mean±standard deviation, APACHE = Acute Physiology and Chronic Health Evaluation, GCS = Glasgow Coma Scale, ICU = Intensive Care Unit, IICU = Intermediate Intensive Care Unit

up and treated in IICU died. 35 (67.3%) patients were transferred to another clinic or discharged home. Demographic data and comorbidities are shown in Table 1. Eleven (21.2%) patients accepted to IICU had more than two comorbidities.

Age, APACHE II and GCS scores, tertiary ICU, and IICU length of stay were compared between groups (Table 2). The mean age in Group 1 was greater than in Group 2, but it was not statistically significant. The APACHE II score was higher but not statistically different in Group 1 patients. GCS was statistically lower in Group 1 than in Group 2 (p = 0.002). There was no statistically significance between the groups regarding the patient's length of stay in the tertiary level ICU and IICU.

Respiratory support applied to patients in IICU were mask/nasal oxygen, noninvasive ventilation (NIV) and, high flow oxygen (HFO), MV support (Table 3). MV support was higher in Group 1 than in Group 2 (82.3% vs. 48.6%, respectively, p = 0.034). Enteral nutritional support was administered to the patients via oral, nasogastric tube, and PEG. Parenteral nutrition support was applied to two (5.7%) patients in Group 2. The need for inotropic agents was 76.5% in Group 1 and 5.7% in Group 2 and it was statistically significant ($p < 0.001$) (Table 3). Physical therapy and

Table 3. Comparison of follow-up and treatments in IICU of the groups

Parameters	Group 1 (n = 17)	Group 2 (n = 35)
Airway		
Respiratory Support		
Mask-nasal O_2 (2-6 Lt/min) n (%)	1 (5.9)	15 (42.8)
HFO n(%)	1 (5.9)	2 (5.7)
NIV n(%)	1 (5.9)	1(2.9)
MV n(%)	14 (82.3)	17 (48.6)
Nutrition support		
Orally n(%)	6 (35.3)	22 (62.9)
Nasogastric tube-PEG n (%)	11 (64.7)	11 (31.4)
Parenteral n (%)	-	2 (5.7)
Inotropic agent requirement	13 (76.5)	2 (5.7)
Physical therapy and rehabilitation n(%)	9 (52.9)	28 (80.0)

HFO = High Flow Nasal Oxygen theraphy, NIV = Noninvaziv ventilation, MV = Mechanical ventilation, PEG = Percutaneous Endoscopic Gastrostomy

rehabilitation support was applied to 9 (52.9%) patients in Group 1 and 28 (80%) patients in Group 2 (Table 3). Among all patients in IICU, percutaneous tracheostomy and PEG were performed in 5 (9.6%) and 4 (7.7%) patients, respectively.

Complications that occurred in IICU were sepsis, multiple organ dysfunction syndromes (MODS), pressure ulcers, cardiac complications, peripheral neuropathy, cerebrovascular accident (CVO), and other infections (Table 4). Sepsis was observed in 35.3% in Group 1 and 22.9% of patients in Group 2. The incidence of MODS was 47.0% in Group 1 and 2.9% in Group 2. Pressure ulcers were present in 82.3% in Group 1 and 60% of patients in Group 2 (Table 4). Negative pressure wound treatment was applied to 5 patients (9.6%) due to pressure ulcers. In addition, 1 patient (1.9%) was treated surgically by debridement and tissue grafting.

DISCUSSION

In recent years, IICU units have been established for patients with respiratory problems in European countries. The primary use of intermediate care units before the pandemic is the treatment of hypercapnic or hypoxemic acute and chronic respiratory failure. In addition, the names of these units were reported as respiratory high dependency units [3]. The IICU is crucial because it is a transfer step between the ICU and the clinical service. In our study, 52 patients who were transferred from the 3rd Level ICU to the IICU after Covid-19 pneumonia were evaluated. 67.3% of the patients were discharged home or to the service. Over time, COVID-19 infection reveals persistent symptoms and a clinical condition such as MODS[5]. These prolong the ICU stay and increase the need for ICU. Therefore, IICUs were used for follow-up and treatment during the COVID-19 pandemic, and the studies conducted in these units contributed to the literature [6-8]. There was no IICU in our hospital before the pandemic. However, during the pandemic, a second-level IICU was created in our hospital for patients with comorbidities who continue to need intensive care. A team of intensive care specialists, nurses, dietitians, and physiotherapists served in this unit. All patients who were hospitalized and followed up in the IICU in our hospital were negative for PCR tests. In addition, our patients were admitted from the tertiary level ICU, whose infection continued and who needed supportive treatment due to additional comorbidities. Matute-Villacís *et al*. discussed the clinical features and outcomes of the patients during the pandemic in IICU [7]. They stated that 61% of the patients were accepted from the ICU, and the other patients were accepted from the ward or emergency room.

Carpagnano *et al*. [6] retrospectively evaluated 87 patients with a diagnosis of COVID-19 who were admitted to the IICU between March 11 and April 17, 2020. They administered NIV therapy to these patients. The patients were transferred to the tertiary level ICU in the necessary clinical conditions. They found that the mortality rate before March 29, 2020 (52.2%), was statistically higher than patients hospitalized after this date (17.1%). They emphasized the reasons for this as the advances in the treatments ap-

Table 4. Complications seen at the groups in IICU

Parameters	Group 1 (n = 17)	Group 2 (n = 35)
Sepsis, n (%)	6 (35.3)	8 (22.9)
MODS, n (%)	8 (47.1)	1 (2.9)
Pressure ulcers, n (%)	14 (82.3)	21(60)
Arrhythmia/heart failure, n (%)	1/1 (11.8)	1/3(11.4)
Peripheral neuropathy, n (%)	0 (0)	2 (5.7)
CVD, n (%)	1 (5.9)	0 (0)
Other Infections, n (%)	7 (41.2)	10 (28.6)

MODS = Multiple organ dysfunction syndrome, CVD = Cerebrovascular disease

plied, the location of IICUs closer to the tertiary level ICU, the creation of a multidisciplinary staff, the increase in the number of health professionals, and the advanced clinical experience. The mortality rate was 32.7% in 52 patients examined in our study. Our result has not been investigated periodically as in the study of Carpagnano *et al*. [6], and the mortality rate in our study was between 52.2% and 17.1%. At the same time period, the mortality rate of patients in the Covid-19 ICU in our hospital was approximately 61%.

Worse clinical outcomes and prolonged hospitalization are observed in patients with COVID-19 pneumonia and comorbidities [9]. Matute-Villacís *et al*. [7] established two new IICUs during the pandemic and discussed patients' clinical features and outcomes. They found that the mean age of the patients was 66 ± 12 years, and hypertension was the most common comorbidity [7]. The mean age of all patients in our study was 70.55 years. The most common comorbidity is multiple comorbidities. The rate of patients with more than two comorbidities (DM, COPD, CVD, and HT) is 21.2%. While Matute-Villacís *et al*. [7] reported the patients' hospital stay as 34 days and the duration of IICU hospitalization as 7 days [7], the IICU hospitalization period was 14.64 days in Group 1 and 20.91 days in Group 2 in our study. Therefore, we think that the length of IICU hospitalization in our study is due to multiple comorbidities in our patients and the long duration of clinical organization.

The mean APACHE 2 score and GCS score are important in determining the prognosis of intensive care unit patients. A high APACHE score and low GCS value are associated with poor prognosis [10]. In our patients, the mean APACHE 2 score was higher, and GCS was lower in the group, resulting in mortality (Group 1). Furthermore, the decrease in GCS value was found statistically significant.

Hernandez-Rubio *et al*. [8] evaluated the outcomes of COVID-19 patients admitted to IICU in their prospective cohort study. In their study, which included 70 patients, the respiratory supports applied to the patients were NIV, HFO, nasal oxygen therapy, and mechanical ventilation. They also reported that the rate of patients who underwent intubation was 37.1%. In addition, they found the mortality rate to be 53.8% in the intubated patient group and 6.8% in the non-intubated group. In our study, respiratory supports used in IICU were mask/nasal oxygen, NIV, HFO, and mechanical ventilation, in line with the literature. Mechanical ventilation support was higher in Group 1 in our study. In our IICU, respiratory support was performed on 4 patients with tracheostomy, and nutritional support was applied to 5 patients by PEG procedure.

There are recommendations regarding the nutrition of COVID-19 patients in the ICU in the literature. Enteral nutrition therapy is primarily recommended for patients requiring invasive mechanical ventilation in the ICU [11, 12]. In our study, enteral and oral nutrition was applied to the patients mostly, and parenteral nutrition was used to only two unsuitable patients.

The most common ICU complications related to COVID-19 are acute respiratory distress syndrome (ARDS) [13] and ICU-induced neuromuscular weakness [14]. Early onset physiotherapy in ICU is an important therapeutic tool to reduce the complications of immobilization. Rehabilitation has been widely recommended in people with COVID-19 pneumonia [15]. In a meta-analysis examining the effect of physical therapy on COVID-19-related disorders, it was reported that physical therapy had positive effects on lung function, physical function, and psychosocial function [16]. Another study concluded that respiratory physiotherapy and physical rehabilitation practices in COVID-19 patients in ICU reduced ICU-related complications and increased patients' quality of life [17]. In our study, physical therapy was applied to more patients in Group 2 than in Group 1 (52.9% vs. 80%, respectively). Because physical therapy was not performed on hemodynamically unstable patients in our hospital.

Pressure ulcers also affect the quality of life in the ICU. The hospital stay is prolonged due to wound care, debridement, and graft procedures [18]. In the literature, the most common areas of pressure ulcers due to supine positions are sacral (50%), heel (15%), and trochanteric (10%). The effect of tissue damage secondary to COVID-19 inflammation is also significant in the etiology of decubitus ulcers [19]. Recent epidemiological data from a primary health center in New York showed that the prevalence of pressure ulcers among COVID-19 patients requiring intensive care is three times higher than that of other non-COVID-19 patients requiring intensive care [20]. In a study, 445 COVID-19 patients were evaluated retro-

spectively for pressure ulcers, and the incidence of pressure ulcers was found to be 46.74%. They stated that age, Braden score, body mass index, comorbidity, DM, fecal incontinence, GCS, use of vasopressor agents, and length of hospital stay were significantly associated with pressure sores [21]. In a different study, including 111 patients hospitalized in the tertiary level ICU with the diagnosis of COVID-19, it was published that 56.8% of the patients had pressure injuries, and the average length of stay was 11.6±9.4 days. The same study stated that 77% of the patients had an additional disease other than COVID-19 [22]. In our study, the rate of pressure ulcers was 82.3% in Group 1 and 60% in Group 2. We attribute the reason why the rate of patients with pressure ulcers is slightly higher than in the literature to the fact that our patients were transferred from the tertiary level ICU and the length of their total ICU stay. In addition, physiotherapy could not be applied due to pandemic conditions in our tertiary level ICU. We think that a higher rate of patient's comorbidities is effective in the formation of pressure ulcers.

A study examining the results of COVID-19 pneumonia patients in the ICU treated with a standard protocol stated that the most common complication was neurological complications, with a rate of 37.66%. Other common complications in these patient groups were reported as infections (28.6% pneumonia, 16.9% sepsis, 14.3% urinary tract infection) and 11.7% as pneumothorax and pneumomediastinum [23]. Hernandez-Rubio *et al*. [8] stated that major medical complications (myocardial injury, hypertension, acute renal failure, bacteremia, septic shock, hospital pneumonia, bronchial obstruction, anemia, thrombocytopenia, and skin ulcers) occurred in 58.6% of patients diagnosed with COVID-19 and admitted to the IICU. In our study, sepsis, one of the most common complications in patients, was observed more frequently in Group 1 than in Group 2 (35.3% vs. 22.9%, respectively). MODS was more common in Group 1 (47.0%) than Group 2 (2.9%) (47.0% vs. 2.9%, respectively).

All patients in our study were admitted to the IICU from tertiary level Covid-19 ICU. Similarly, Matute-Villacís *et al*. [7] reported that most patients (61%) admitted to the IICU were transferred from the tertiary level ICU. They reported that the prominent role of an IICU during a pandemic is to provide rapid discharge and alleviate the tertiary level ICU burden. In addition, IICU is multidisciplinary care that shortens the length of stay in the intensive care unit and potentially shortens the hospital stay [7]. A multidisciplinary approach was applied for nutrition, physiotherapy and decubitus ulcer care in IICU.

Limitations

The limitations of our study are the number of patients and the retrospective nature. In addition, the long-term consequences of COVID-19 could not be evaluated.

CONCLUSION

Consequently, ensuring patient discharge from the tertiary level ICU for relieving high ICU load and allowing bed's turnover during the pandemic is essential. IICU provides effective treatment with multidisciplinary care and is needed to rehabilitate patients who continue to need intensive care.

Authors' Contribution

Study Conception: FA, CY; Study Design: FA, CY; Supervision: FA; Funding: ANB; Materials: TO, CSA; Data Collection and/or Processing: CSA, FA; Statistical Analysis and/or Data Interpretation: ÜK; Literature Review: BÖ, FA; Manuscript Preparation: FA, CY and Critical Review: CY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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