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Clinical features and predisposing factors of delirium due to COVID-19 pneumonia in intensive care units

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Abstract. – OBJECTIVE: Delirium is an acute disorder in which attention, perception, memory, thought, mood, psychomotor activity and sleep-wake cycles change rapidly. Delirium is also a common clinical syndrome in patients hospitalized in intensive care units due to COVID-19 pneumonia. We reviewed clinical features and predisposing factors of delirium according to psychomotor subtype in patients hospitalized in the intensive care units due to COVID-19 pneumonia.

PATIENTS AND METHODS: 64 patients who were hospitalized in the intensive care units due to COVID-19 pneumonia were included. Delirium status and psychomotor subtype were determined by applying the Confusion Assessment Method for the Intensive Care Unit scale to the patients daily. The gender, age, comorbidity, treatments, intubation, and mortality rates of the patients were recorded. Multivariate analyses were performed by examining predisposing factors, arterial blood gases, hemograms, biochemistry, and brain magnetic resonance imaging.

RESULTS: There were 64 patients in delirium clinic, 65.6% (n=42) of them were male. Hypokinetic delirium was more common in 60.9% (n=39). 79.4% of the patients who received ventilator support were male (p=0.013).When mortality was analyzed in this group, hypoactive delirium was found to be significantly higher (p=0.035). In addition, leukocyte levels were higher in patients with hypokinetic delirium (p=0.029). Ferritin and fibrinogen levels were higher in patients with hyperkinetic delirium (p=0.039, p=0.008, respectively).

CONCLUSIONS: The presence of additional diseases such as advanced age, male gender, hypertension, coronary artery disease, dementia, and hypoxia were factors that increased the frequency of delirium. In addition, the mortality rate was higher in patients with hypokinetic delirium.

Key Words:
COVID-19, Pneumonia, Delirium, Mortality.

Introduction

The COVID-19 (SARS-CoV-2) virus first appeared in Wuhan, China with several cases of pneumonia of unknown etiology in December 2019 and caused a rapidly spreading global pandemic[1,2].In the early stages of this pneumonia developed severe acute respiratory infection symptoms, acute respiratory distress syndrome (ARDS), and other serious complications in some patients[2]. As case reports increased, it was observed that COVID-19 not only caused respiratory problems, but also various symptoms and findings involving the cardiac, hematological, thromboembolic, and neurological systems. The most common neurological findings are headache, myalgia, fatigue, delirium, and cerebrovascular events[3].

Delirium is defined as an acute condition characterized by mental confusion and emotional disruption[4]. In the Intensive Care Unit (ICU), it is one of the most common behavioral manifestations of acute brain dysfunction[5]. Delirium is defined as changes in consciousness that fluctuate throughout the day; it is classified as either hypokinetic or hyperkinetic delirium[6]. Delirium is more common in elderly patients compared to the normal population, especially during hospitalization[7,8]. Delirium is an important health problem that increases recovery time and hospital costs[9]. It has been reported that delirium is a common clinical syndrome accompanying SARS-CoV-2 disease. Many factors may be responsible for the

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pathogenesis of delirium[10]. In SARS-CoV-2 pneumonia in particular, factors that can increase the likelihood of delirium include hospitalization in an intensive care unit, strict isolation, medications, the severity of the infection, hypoxia, and noninvasive mechanical ventilation support[10].

In this study, patients with SARS-CoV-2 pneumonia in the intensive care units of our hospital were evaluated, and patients with delirium were included in the study. In particular, mortality and length of hospital stay were evaluated in these patients, and the contributing factors were investigated according to the psychomotor subgroup of delirium.

Patients and Methods

Ethical Approval and Patient Selection

As the first positive case was diagnosed in our hospital on 23 March 2020, the files of the patients who were admitted to the intensive care unit of Malatya Training and Research Hospital with the diagnosis of SARS-CoV-2 pneumonia between 23 March 2020 and 23 July 2020 were retrospectively scanned through the hospital information system. This study was conducted after approval was obtained from the Malatya Clinical Research Ethics Committee (decision number 2020/200, dated 23.12.2020).

CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) tests were administered daily to patients given neurology consultations due to acute changes in consciousness. During the study period, 64 of 550 SARS-CoV-2 patients with pneumonia who had neurology consultations were diagnosed with delirium. Patients with changes in consciousness who did not meet DSM-V criteria, were not evaluated with the CAM-ICU scale, did not have central imaging performed, and did not have neurology consultations were excluded from the study.

Patients who were diagnosed with delirium were classified according to psychomotor subtype. Age, sex, comorbid diseases, medications used, respiratory support needed, arterial blood gas, complete blood count, serum C-reactive protein (CRP) and biochemistry values, and neurological examination findings were recorded. In addition, the length of hospital stay, mortality, and discharge status of the patients were analyzed. Magnetic resonance imaging (MRI) of the central nervous system findings of all patients were compared according to delirium subtype.

Statistical Analysis

The data were analyzed using the SPSS Statistics program (version 22.0; IBM Corp., Armonk, NY, USA). The numerical data were expressed as mean and standard deviation (SD), and the categorical data were expressed as number (n) and percentage (%). Statistical analyses of the categorical variables were performed with the Pearson's Chi-square test. Independent variables (age values and hospitalization periods) that did not fit the normal distribution were analyzed by using the Mann-Whitney U test and nonparametric tests. A value of $p<0.05$ was considered statistically significant.

Results

550 COVID-19 patients hospitalized in the intensive care unit were examined. Of these 550 patients, 64 patients in the delirium clinic were included in the study. The mean age of the patients was 78.5 (13.9) years; 65.6% (n=42) were male and 34.4% (n=22) were female (Table I).When comorbidities were examined in these patients, 41 patients (64.1%) had hypertension, 29 patients (45.3%) had coronary artery diseases, 24 patients (37.5%) had dementia, 20 patients (31.2%) had cerebrovascular diseases, 18 patients (28.1%) had heart failure, and 17 patients (26.6%) had diabetes mellitus. When the delirium status of the 64 patients was evaluated according to subtype, it was found that the rate of hyperkinetic delirium was 39.1% (n=25) and the rate of hypokinetic delirium was 60.9% (n=39). It was found that 53.1% (n=34) of the patients were intubated and 46.9% (n=30) were not intubated; 79.4% (n=27) of the intubated patients were males. The sex difference on intubated patients was statistically significant ($p=0.013$) (Table I). When mortality rates were examined, it was seen that 46.9% (n=30) of the patients died while they were intubated; 73.3% (n=22) of these patients were in hypokinetic delirium and 26.7% (n=8) were in hyperkinetic delirium. The difference was found to be statistically significant ($p=0.035$) (Table II).

When we examined the neurological findings of the patients, it was found that 25 (39.0%) patients were agitated;39 (60.9%) patients were unresponsive, ranging between lethargy, stupor, and coma. When the MRI results of the patients were examined by the delirium clinic, the most common findings were cortical atrophy in 22 (34.3%) patients, followed by infarct area in 20 (31.2%)

Table I. Demographic and clinical data of delirium patients.

Variables	Data	n (%)
Sex	Male	42 (65.6%)
	Female	22 (34.4%)
Medication	Favipiravir	29 (45.3%)
	Dexamethasone	36 (56.3%)
	Hydroxychloroquine sulfate	49 (76.6%)
Status of Intubation	Intubated	34 (53.1%)
	Non-intubated	30 (46.9%)
Mortality	Exitus	30 (46.9%)
	Survivor	34 (53.1%)
Delirium subtype	Hypokinetic	39 (60.9%)
	Hyperkinetic	25 (39.1%)
Comorbidities	Hypertension	41 (64.1%)
	Coronary Artery Disease	29 (45.3%)
	Dementia	24 (37.5%)
	Cerebrovascular Disease	20 (31.2%)
	Heart Failure	18 (28.1%)
	Diabetes Mellitus	17 (26.6%)
	Chronic Obstructive Pulmonary Disease	12 (18.7%)

patients, and periventricular ischemic gliotic area in 17 (26.5%) patients (Table II). The infarct finding was significantly higher in MRI images of patients with hypokinetic delirium. However, there were no significant relationships between the kinetic status of delirium and other MRI findings (p>0.05) (Table II).

The mean length of stay in the ICU, sex, intubation status, mortality, and delirium subtype were analyzed. We found that the mean length of stay in the intensive care unit was 13.12 (12.64) days for male patients and 14.95 (14.22) days for female patients. Female patients stayed in the ICU longer than males; however, the difference was not statistically significant (Table III). When the length of stay was compared according to intubation status and mortality, there was no statistically significant difference (p=0.596) (Table III). It was observed that patients with hypokinetic delirium required longer stays in the ICU than hyperkinetic delirium patients; however, the difference was not statistically significant (p=0.447) (Table III).

The medications given for the treatment of SARS-CoV-2 in delirium patients were also examined. No sedative medication was used for the patients who were not intubated. Rocuronium and midazolam were administered intravenously during intubation, whereas benzodiazepine treatment was not administered. In the treatment of SARS-CoV-2, it was observed that hydroxychloroquine sulfate 2 × 200 mg/day was the most common medication administered, with a high rate of 76.6% (Table II). In addition, it was observed that 76.4% (n=26) of intubated patients

Table II. The distribution of the clinical data according to delirium subtype.

Patient Characteristics	Hypokinetic Delirium (n=39, 60.9%)	Hyperkinetic Delirium (n=25, 39.1%)	p-value
Sex			
Male	25 (59.5%)	17 (40.4%)	0.749
Female	14 (63.6%)	8 (36.3%)	
Intubation	24 (70.5%)	10 (29.4%)	0.056
Exitus	22 (73.3%)	8 (26.7%)	0.035
Stay in the ICU (days)	13.3	12.9	0.447
MRI findings			
Normal	3	2	
Periventricular ischemic gliotic areas	10	7	0.243
Infarct areas	16	4	
Cortical atrophy	10	12	

Table III. The comparison of length of stay according to subtype of delirium, sex, and clinical status.

Patient Characteristics	n (%)	Stay in the ICU (days) Mean (S.D.)	p*
Sex			0.596
Male	42 (65.6)	13.12 (12.64)	
Female	22 (34.4)	14.95 (14.22)	0.791
Intubated	34 (53.1)	15.06 (15.96)	0.231
Exitus	30 (46.8)	13.16 (14.97)	
Delirium subtype			0.447
Hypokinetic	39 (60.9)	14.05 (14.15)	
Hyperkinetic	25 (39.1)	13.33 (11.82)	

n: number; %: percentage; *: Mann-Whitney U test.

and 83.3% (n=25) of the patients who died were treated with dexamethasone (6 mg/day). The rate was statistically significant in the patient groups who were intubated and died ($p<0.001$; $p<0.001$, respectively) (Table IV). Considering the distribution of medication regimens by sex, it was found that favipiravir treatment (2 × 1600 mg/day on the first day, 2 × 600 mg/day on subsequent days) was statistically significantly more commonly administered to male patients than to female patients ($p=0.036$) (Table IV). There was no statistical difference between the patients according to the kinetic status of delirium in terms of administered medications ($p>0.05$) (Table IV).

The laboratory findings, including arterial blood gases, complete blood count (CBC), biochemistry, and CRP levels, of the patients during the period when delirium was detected were examined. Partial oxygen pressure (PO_2) [48.98(15.26), 48.97 (14.38), respectively] and saturation (SpO_2) [74.64 (13.88), 74.25 (15.83), respectively] levels were found to be significantly lower in both hypokinetic delirium and hyperkinetic delirium patients, which is consistent with hypoxia. In addition, when compared according to kinetic status of delirium, leukocyte levels were found to be higher in patients with hypokinetic delirium ($p=0.029$), and ferritin and fibrinogen levels were higher in patients with hyperkinetic delirium. Both results were statistically significant according to the Chi-square test ($p=0.039$ and $p=0.008$, respectively) (Table V). There were no significant differences between the delirium subtypes in terms of partial carbon dioxide pressure (PCO2), serum pH, lymphocyte, platelet, D-dimer, and CRP levels (Table V).

Discussion

Coronaviruses constitute a large group of enveloped single-stranded RNA viruses. Before 2019, when novel coronavirus SARS-CoV-2 was identified, 6 members of the coronavirus group, including HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS (severe acute respiratory syndrome), and MERS (Middle East Respiratory Syndrome), had been identified[11]. Coronaviruses (CoVs) have been known to exhibit neurotrophic and neuroinvasive properties[12]. Similarly, it has been observed that SARS-CoV-2 binds to

Table IV. Relationship between medication regimens and clinical variables in the treatment of SARS-CoV-2.

Patient Characteristics	Favipiravir	Dexamethasone	Hydroxychloroquine sulphate	pβ
Age [Mean (SD)]	71.90 (14.26)	74.67 (13.86)	75.00 (12.88)	>0.05
Male patients (n, %)	23 (79.3) [a]	27 (75.0) [b]	31 (63.2) [b]	0.036
Intubated (n, %)	18 (62.1) [b]	26 (72.2) [a]	25 (51.0) [b]	<0.001
Exitus (n, %)	17 (58.6) [b]	25 (69.4) [a]	21 (42.8) [b]	<0.001
Delirium subtype				
Hypokinetic (n, %)	17 (58.6)	25 (69.4)	29 (59.1)	>0.05
Hyperkinetic (n, %)	12 (41.4)	11 (30.6)	20 (40.9)	

The superscripts a or b indicate that the difference between the groups is significant in terms of the indicated variables β: Pearson's chi-square test.

Table V. Comparison of ABG and CBC levels in patients with hypokinetic and hyperkinetic delirium.

Blood Parameters	Hypokinetic Delirium Mean (SD)	Hyperkinetic Delirium Mean (SD)	p*
pH	7.36 (0.98)	7.33 (0.11)	0.235
PO_2	48.98 (15.26)	48.97 (14.38)	0.491
SpO_2	74.64 (13.88)	74.25 (15.83)	0.265
PCO_2	40.96 (15.74)	42.01 (11.55)	0.180
WBC	13.17 (10.58)	12.02 (6.15)	0.029
Lymphocyte	13.25 (10.49)	10.66 (8.25)	0.825
Thrombocyte	193.19 (118.47)	242.00 (123.11)	0.057
Ferritin	522.85 (530.38)	544.19 (589.65)	0.039
D-dimer	4.18 (4.20)	3.60 (5.14)	0.424
Fibrinogen	405.30 (190.99)	468.09 (213.89)	0.008
CRP	10.15 (8.62)	11.22 (8.82)	0.144

Mean (SD): standard deviation; *Pearson's Chi-square test; CRP: C-reactive protein.

ACE-2 receptors in the central nervous system (CNS) capillary endothelium *via* Spike-1 (S1) protein and the virus invades the cell, which leads to neuroinvasion[13]. In addition, ACE2 receptors, which are intensely expressed in the lungs, have also been shown to be expressed significantly in some regions of the brain, such as the substantia nigra and/or brain ventricles, although general expression in the brain is low[14]. In the same studies[14], it has been shown that ACE2 receptors are expressed at high levels in dopaminergic nuclei including the ventral tegmental area and substantia nigra, serotonergic nuclei including midbrain raphe nuclei, histaminergic nuclei including the tuberomammillary nucleus, and the norepinephrinergic locus coeruleus[14]. Based on these studies, it has been suggested that neurological disorders that directly or indirectly involve the CNS, peripheral nervous system (PNS), or muscle system, as well as respiratory problems, can develop during the SARS-CoV-2 pandemic[15].

In patient series conducted during the SARS-CoV-2 pandemic, it has been reported that mental status changes, including delirium, are observed with significant frequency[14]. Delirium can be divided into three subtypes – hyperactive (mania), hypoactive (depressive), and mixed (mixed) – depending on the prominent psychomotor characteristics[6]. In this study, patients with delirium were grouped into hypokinetic and hyperkinetic subtypes according to the relevant mental changes; the mixed subtype was not observed in our patients.

The symptoms of delirium and confusion may result from an acute biological process at the structural, functional, and/or chemical levels in the brain; more importantly, it may result from a pathologic process existing outside the brain or from acute predisposing factors leading to neurotransmitter, neuroendocrine, and/or neuroinflammation cascades[16]. Kotfis et al[10] suggested various mechanisms including direct CNS invasion, induction of CNS inflammatory mediators, secondary effects due to other organ damage, sedation strategies, prolonged mechanical ventilation duration, immobilization, separation from other family members, and strict isolation measures may be responsible for the pathogenesis of delirium seen in SARS-CoV-2 patients in the ICU[10]. In addition, in recent mRNA studies that have had remarkable molecular results, it has been suggested that dopadecarboxylase may functionally affect dopamine and serotonin synthesis by binding with ACE2 receptors; therefore, it has been suggested that dopadecarboxylase may cause delirium by causing direct viral invasion[14].

Delirium is a common clinical syndrome that can be observed during hospitalization, especially in elderly patients. Feldman et al[7] reported that the incidence of delirium in elderly hospitalized patients was between 14% and 56%[7].In another study, Khurana et al[8] reported that delirium was observed in 27.4% of 400 patients over the age of 60.Duringthe SARS-CoV-2 pandemic, an increase was observed in the number of patients with delirium in clinics and especially in ICUs. Kennedy et al[9] examined 817 SARS-CoV-2 patients who were admitted to an emergency department with a delirium clinic; they reported that the average age was 77.7 and delirium was present in 226 (28%) patients at the time of admission to the ED. In another study[17], 707 patients aged 50 years and older who were hospitalized with a diagnosis of SARS-CoV-2 were reviewed; delirium was detected in 234 (33%) patients[17].These varying

results may be due to the missed diagnosis of delirium due to difficulties in diagnosis, especially due to the decrease in affect and communication ability of patients with hypokinetic delirium. In our study, the number of patients evaluated for delirium was lower than in the literature studies (11.63%). We attribute this situation to the under diagnosis of delirium compared to respiratory and metabolic problems in intensive care units. In our study, the high rate of patients with hypokinetic delirium may support this suggestion (60.93%).

An age over 75 years [n=459 (56%)], history of using psychoactive drugs [n=464 (57%)], vision or hearing loss [n=59(7%) and n=54(7%) respectively], dementia [n=248 (30%)], stroke [n=107(13%)], or a diagnosis of Parkinson's disease [n=23 (3%)] are reported to be significant risk factors for delirium[9]. In addition, delirium was found to be associated with a prolonged duration of stay in the ICU and higher mortality rates[9]. In our study, the mean age of patients with delirium was found to be 78.5 (13.9) and advanced age was a risk factor for delirium. In addition, in our study, hypertension was found to be the most common comorbid disease in delirium associated with SARS-CoV-2 infection. When medication regimes were compared in SARS-CoV-2 patients, it was observed that hydroxychloroquine sulfate and favipiravir were most commonly used in our patients, with no significant effect detected on the development of delirium; however, the rate of intubation and mortality was significantly higher in patients using dexamethasone. This situation may be associated with the fact that dexamethasone therapy is frequently administered to patients with severe lung involvement and hypoxia.

Studies[18,19] to examine sex differences in patients with SARS-CoV-2 have been performed. Jin et al[18] reported that the rates of female and male patients with SARS-CoV-2 were similar. However, the rates of males among seriously ill patients and for mortality were reported to be 2.4 times higher than those of females (70.3%*vs.* 29.7%, p=0.016)[18]. In a comprehensive meta-analysis study conducted by Peckham et al[19], it was reported that rates of males and females were similar in SARS-CoV-2 disease-positive patients, whereas the rate of those hospitalized in the ICU and the rate of mortality were 3 times higher in males than in females. In our study, the rate of males was higher in the ICU; however, the difference was not significant. The fact that only ICU patients were included in the study may have affected this finding. Male sex was statistically significantly higher in intubated patients (p=0.013).

SARS-CoV-2 infection has been found to be associated with an increased risk of cognitive impairment and death up to 12months after discharge from the ICU[20]. Delirium is an important public health problem and has been associated with long-term cognitive impairment[21]. Li et al[22] suggested that the presence of delirium in SARS-CoV-2 pneumonia may be a determining factor for the prognosis of the disease. They showed that early detection of delirium in SARS-CoV-2 patients may be an early sign of worsening respiratory failure, or an indicator of additional organ failure or neuroinvasive spread of SARS-CoV-2 into the CNS[22]. Kotfis et al[23] found that delirium may be a symptom of prodromal infection or hypoxia associated with respiratory failure. In the same study[23], it was concluded that the virus can spread faster *via* aerosol due to coughing due to the agitation of hyperactive delirium patients. It has been reported that patients with non-agitated hypoactive delirium may be more frequentlyoverlooked[23]. In our study, it was observed that hypoxia and hypoxemia findings were evident in the arterial blood gas analyses of the patients in terms of predisposing factors for delirium. Findings consistent with marked hypoxia were present in both hypokinetic and hyperkinetic delirium cases; however, the difference was not significant. The infection parameters were high in both groups; however, there were no significant differences between the groups in terms of PCO_2 and CRP levels. On the other hand, leukopenia, ferritin, and fibrinogen levels were found to be significantly higher in patients with hyperkinetic delirium compared to those with hypokinetic delirium.

In a study conducted by Ely et al[24] in 2004, it was reported that delirium is a strong predictor for ICU admission, 6-month mortality, and prolonged hospital stay. In other studies[20,24,25], it has been reported that the rate of delirium in ICU patients undergoing mechanical ventilation increased up to 70-75%; this situation was associated with prolonged hospital stay, increased risk of mortality, higher costs, and cognitive loss after hospitalization[20,24,25]. In our study, no significant difference was found between delirium subtypes in terms of stay in the hospital, sex, or intubation status. However, mortality was found to be significantly higher in male patients with delirium. In addition, the mortality rate in patients with hypokinetic delirium was found to be 2.75 times higher than that of patients with hyperkinetic delirium.

In their study, Raman et al[26] reported that pulmonary, cardiovascular, neurological, and psy-

chiatric conditions of patients deteriorated after SARS-CoV-2 infection. They showed that there were tissue changes in the thalamus, posterior thalamic radiations, and sagittal stratum regions 2-3 months after the onset of the disease in the MRI images of SARS-CoV-2 patients who had recovered, accompanied by cognitive losses such as deficiencies in executive function and visual-spatial processing[26]. In our study the most common finding in the MRI images of the patients was diffuse cortical atrophy (36.1%), which suggests that mild cognitive symptoms that may exist in patients of advanced age before the diagnosis of SARS-CoV-2 infection may become more pronounced after the diagnosis. Therefore, closer follow-up of patients in terms of delirium may help reduce the development of consequent cognitive loss and social problems.

In a study of 71 patients by Callea et al[27] in Italy, delirium was detected in 20 (28.2%) patients. Of these 20 patients (100%), 10 (50%) were hypokinetic, 4 (20%) were hyperkinetic, and 6 (30%) had mixed type delirium[27]. In our study, 39 (60.9%) patients were in the hypokinetic and 25 (39.1%) hyperkinetic delirium clinics. Our rates of hypokinetic and hyperkinetic patients were similar to those in the literature[27]. In a study[28] examining neurological symptoms in COVID-19 patients in Turkey, 31 (11%) of 282 COVID-19 patients had delirium. Twenty (7.1%) of these patients were hospitalized in the intensive care unit and 11 (3.9%) were hospitalized in the ward. Of these 31 (100%) patients with delirium, 15 (48%) died[28]. In our study, 30 (46.8) of 64 (100%) delirium patients died, and this rate was close to literature[28].

This study has some limitations. The fact that only patients hospitalized in the intensive care unit were included in our study and the higher rate of ICU admission for male patients may have led to a higher rate of male patients presenting with delirium. This study is a preliminary study; evaluation of all patients in the ICU in terms of delirium criteria will contribute to clarifying the effects of the subtype of delirium on the prognosis.

Conclusions

Delirium is a condition generally associated with length of stay, mortality, and cognitive impairment. The increased need for ICU admission during the SARS-CoV-2 pandemic has also led to an increase in delirium cases seen in intensive care units. In this study, it was noted that advanced age, male sex, and the presence of additional diseases such as hypertension, coronary artery disease, dementia, and hypoxia are factors that increase the frequency of delirium. The rate of mortality was higher in males and patients with hypokinetic delirium. The levels of leukopenia, fibrinogen, and ferritin were higher in patients with hyperkinetic delirium compared to those with hypokinetic delirium.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Ethical Approval

This study was approved by the Malatya Clinical Research Ethics Committee with the decision number 2020/200, dated 23.12.2020.

Informed Consent

Informed consent was obtained.

Authors' Contributions

TE, ME, IT, LS and LAD: Concept and design of study or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published.

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