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Does the variant positivity and negativity affect the clinical course in COVID-19?

A cohort study

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Abstract

The primary aim of the current study is to analyze the clinical, laboratory, and demographic data comparing the patients with Coronavirus Disease 2019 (COVID-19) admitted to our intensive care unit before and after the UK variant was first diagnosed in December 2020. The secondary objective was to describe a treatment approach for COVID-19. Between Mar 12, 2020, and Jun 22, 2021, 159 patients with COVID-19 were allocated into 2 groups: the variant negative group (77 patients before December 2020) and the variant positive group (82 patients after December 2020). The statistical analyses included early and late complications, demographic data, symptoms, comorbidities, intubation and mortality rates, and treatment options. Regarding early complications, unilateral pneumonia was more common in the variant (–) group ($P = .019$), whereas bilateral pneumonia was more common in the variant (+) group ($P < .001$). Regarding late complications, only cytomegalovirus pneumonia was observed more frequently in the variant (–) group ($P = .023$), whereas secondary gram (+) infection, pulmonary fibrosis ($P = .048$), acute respiratory distress syndrome (ARDS) ($P = .017$), and septic shock ($P = .051$) were more common in the variant (+) group. The therapeutic approach showed significant differences in the second group such as plasma exchange and extracorporeal membrane oxygenation which is more commonly used in the variant (+) group. Although mortality and intubation rates did not differ between the groups, severe challenging early and late complications were observed mainly in the variant (+) group, necessitating invasive treatment options. We hope that our data from the pandemic will shed light on this field. Regarding the COVID-19 pandemic, it is clear that there is much to be done to deal with future pandemics.

Abbreviations: ARDS = acute respiratory distress syndrome, ARF = acute respiratory failure, CMV = cytomegalovirus, CoV = Coronavirus, COVID-19 = Coronavirus disease 2019, CPAP = continous positive airway pressure, ECMO = extracorporeal membrane oxygenator, HFNC = high flow nasal cannula, ICU = intensive care unit, MAS = macrophage activating syndrome, MOF = multi-organ failure, nCPAP = nasal continous positive airway pressure, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, VV-ECMO = veno venous extracorporeal oxygenator.

Keywords: complications, Coronavirus disease 19, COVID-19 variants, mortality, SARS-CoV-2

1. Introduction

Coronavirus (CoV) causes various human respiratory tract infections ranging from mild cold to severe respiratory distress syndrome.[1]

CoVs were first discovered in the 1960s. The most severe types resulting in large-scale pandemics in the past are SARS (2002–2003) and the Middle East Respiratory Syndrome (in 2012).[2,3]

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of Hisar Intercontinental Hospital.

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The new CoV disease, also known as severe acute respiratory syndrome coronavirus (SARS-CoV-2) and COVID-19, is an emerging global health threat.[4]

The COVID-19 epidemic started in Wuhan city, China, towards the end of December 2019 and has spread rapidly to neighboring countries in the initial months.[5,6]

In response to the surging numbers of new diagnoses, including an all-time high of 53,000 on December 29, 2020, was detected. In September 2020, in the UK, the variant represented only 1 in 4 new diagnoses of COVID-19, whereas by mid-December, this had increased to almost 2-thirds of the new cases in London. As of December 30, 2020, it had recorded more than 2 million cases of infection and more than 70,000 deaths.[7]

A total of 159 patients with COVID-19 who were admitted to our intensive care unit (ICU) were retrospectively analyzed and discussed in detail. The patients were allocated into 2 groups: before the UK variant was first diagnosed in December 2020 (variant negative) and the second group after December 2020 (variant positive).

We discussed these ICU patients thoroughly regarding admittance date, early and late complications, comorbidities, and treatment options, in addition to demographic data, symptoms, and laboratory findings.

Although this is a small clinical case series study, we believe that our data will shed light on this field and provide hope for treating patients with the upcoming scary COVID-19 variants.

2. Methods

Between Mar 12, 2020, and Jun 22, 2022, 159 patients with COVID-19 who were admitted to the ICU of the Hisar Intercontinental Hospital were included in the study. Of whose data was not reached completely, they are kept out of the study. All parameters were studied for the patients when they were admitted to the ICU till their discharge from the ICU. This study was approved by the Ethics Committee of Hisar Intercontinental Hospital (Local Reference No: 34).

Two cohorts were created for this study. Seventy-seven patients were admitted as variant (–) negative before Dec 31, 2020 (the alpha variant first appeared in the UK). After Dec 31, 2020, an 82-alpha variant (+) positive group was identified.

We statistically compared the 2 cohorts according to demographic characteristics, comorbidities, mortality rate, intubation rate, clinical complaints, laboratory blood data, early complications, late complications, and evaluate for the possible clinical effects of UK variant.

2.1. Statistical analysis

For all statistical analyses, we used R software v. 3.5.1. (R statistical software, Institute for Statistics and Mathematics, Viennae, Austria). Numerical variables are presented as medians and interquartile ranges. Categorical variables are presented as percentages and numbers. The study population was grouped as variant (–) for those admitted to the hospital before December 31, 2020, and variant (+) for those accepted after December 31, 2020. Statistical differences between these 2 groups for continuous variables were analyzed using the Mann–Whitney *U* test, and differences between categorical variables were analyzed using the chi-square or Fisher exact test. A *P* value of < .05 was accepted as the limit for statistical significance.

3. Results

The study included 159 patients hospitalized due to (+) PCR tests and transferred to the ICU between 12.03.2020 and 22.06.2021.

In the whole group, 68 patients died and 77 patients were intubated; these were not statistically different between the groups.

Comparing the variant (+) group to variant (–), the time from occurrence of first symptoms to hospitalization (date1) was 4 days (0–9 days; $P = .111$), time from hospitalization to ICU (date2) was 2 days (0–6 days; $P < .001$), and the time spent in the ICU (date3/ Supplemental Digital Content [Graph1, http://links.lww.com/MD/I563]) was 9 days (3–16 days; $P < .001$).

In the variant (+) group, both date2 and date3 were statistically significantly longer ($P < .001$).

Seven variant (+) patients received extracorporeal membrane oxygenator (ECMO) support. The ECMO period lasted for 1.0 to 1.5 months an average. The mortality rate was 57.14% in 4 patients. Three patients were successfully weaned from ECMO, 2 returned to daily life after ECMO, and 1 patient was alive but was still on treatment for hypoxic encephalopathy.

Hypertension ($P = .004$) and malignancy ($P = .006$) were primarily observed in the variant (+) group.

Other nonsignificant parameters were DM, diabetes mellitus, coronary artery disease, chronic kidney disease, chronic heart failure, atrial fibrillation, asthma, obesity, hyperthyroidism, gout, polycythemia, previous MI, smoking, previous stroke, and previous tuberculosis.

Although the mortality rate was numerically higher in the variant (+) group (41 vs 27), it was not statistically significant ($P = .156$) like the intubation rate ($P = .755$) in either groups (Table 1–Demography and comorbidity).

Fever ($P = .040$), headache ($P < .001$), musculoskeletal pain ($P < .001$), shortness of breath ($P < .001$), fatigue ($P < .001$), and malaise ($P = 00.016$) were more common in the variant (+) group than in the variant (–) group.

Regarding laboratory blood data, only the neutrophil count was significantly higher in the variant (+) group ($P = .020$)* (Supplemental Digital Content [Graph1, http://links.lww.com/MD/I563]).

No significant differences were observed in other laboratory parameters such as lymphocyte count ($P = .067$), D-dimer ($P = .171$), troponin ($P = .678$), platelet count ($P = .224$), ferritin ($P = .500$), procalcitonin ($P = .127$), CRP ($P = .363$), LDH, aspartatae transaminase (AST), alanine transaminase (ALT), urea, creatinine, hemoglobin, and hematocrit values ($P > .05$).

Table 1

Demography & comorbidity.

Demography & comorbidty	Variant (–)	Variant (+)	*P* value
N	77	82	
Age	57.25	60.32	.219*
Sex (M/F)	77/0	63/19	<.001
Hypertension	29 (3.2%)	55 (67.07%)	.004
Malignancy	0 (0.0%)	9 (10.97%)	.006

Hypertension and malignancy were significantly more seen in the variant (+) group.

M = male, F = female.

* nonsignificant.

3.1. In terms of complications

1.3.1. Early complications. The statistically significant complications were unilateral pneumonia (P = .019) in the variant (–) group and bilateral pneumonia (P < .001/ Supplemental Digital Content [Graph1, http://links.lww.com/MD/I563]), cytokine storm (P = .001/ Supplemental Digital Content [Graph2, http://links.lww.com/MD/I564]), and pleural effusion in the variant (+) group (P = .001).

Acute respiratory distress syndrome (ARDS) (Supplemental Digital Content [Graph2, http://links.lww.com/MD/I564]), pneumothorax, chylothorax, and hemothorax were not significantly different between the 2 groups (P > .05) (Table 2 – early complications).

2.3.1. Late complications. Cytomegalovirus (CMV) pneumonia was more common in the variant (–) group (P = .023). Secondary gram (–) infections (P = .016), ARDS (P = .017), fungal infections (P = .037), cerebral/pulmonary embolism (P = .039/ Supplemental Digital Content [Graph2, http://links.lww.com/MD/I564]), bilateral pneumonia (P = .003), pulmonary fibrosis (P = .048/ Supplemental Digital Content [Graph2, http://links.lww.com/MD/I564]), and septic shock (P = .005/ Supplemental Digital Content [Graph1, http://links.lww.com/MD/I563]) were significantly more common in the variant (+) group. In addition, myocarditis (P = .063) and multi-organ failure (MOF) (P = .092) were not significantly more frequently observed in the variant (+) group (Table 3 – late complications).

Other complications such as sepsis (P = .154), secondary gram (+) infections (P = .139), polyneuropathy (P = 1.0), liver failure (P = 1.0), MI (P = .546), pericarditis (P = .175), pericardial effusion (P = .126), vertebral discopathy, and mediastinal emphysema were not significantly different between the groups.

3.2. Therapeutic options

Favipiravir, hydroxychloroquine (Plaquenil), azithromycin, oseltamivir (enfluvir), meropenem, levofloxacin (tavanic), and immune plasma were more commonly used in the variant (–) group (P < .001).

However, colchicine, prednisolon-250 mg (P = .004), sulbactam + cefoperazone (sulperazone) (P = .006), moxifloxacin (Avelox), valganciclovir (Valcyte) (P = .02), pirfenidone, ECMO, and high flow nasal cannula (HFNC) oxygen were more commonly used in the variant (+) group (P < .001) (Table 4 – therapeutic options).

Other medication options, such as Kaletra (lopinavir/ritonavir) (P = .601), Enoxaparin (P = .345), Dexamethasone (P = .525), Vitamin C (P = .735), Targocid (teicoplanin) (P = .932), Amikacin (Amikozit) (P = .073), Triflucan (fluconazole) (P = .908), Bactrim (trimethoprim/sulfamethoxazole) (P = .232), caspofungin (P = .259), linezolid (P = .982), ceftazidime (P = .631), anakinra (Kineret) (P = .932), and tocilizumab (Actemra) (P = .165) were not different in either group.

Additionally, the study groups did not differ significantly in terms of the use of plasmapheresis (P = .701).

Demonstrative and educational images of the CoV complications are shown in 2 separate figures (Fig. 1 CXR and Fig. 2 CT) to explain how radiographically the CoV destroyed the lungs.

4. Discussion

An outbreak of atypical pneumonia caused by a novel CoV was reported in Wuhan, Hubei Province, China, in December 2019.[8,9] The International Committee on Taxonomy of Viruses and the World Health Organization (WHO) later named this CoV and the disease caused by SARS-CoV-2 and COVID-19.

Globally, as of January 4, 2022, 290,959,019 confirmed cases of COVID-19, including 5,446,753 deaths, have been reported to the WHO.[10]

Various modeling exercises have estimated a new variant of SARS-CoV-2 to be up to 70% more transmissible than the previously circulating form of the virus. In September 2020, this

Table 2

Early complications.

Early complications	Variant (–)	Variant (+)	*P* value
N	77	82	
Bilateral pneumonia	38	77	<.001
Unilateral pneumonia	7	0	.019
Cytokine storm	24	52	.001
Pleural effusion	4	19	.001

The statistically significant complications were unilateral pneumonia in the Variant (–) group, whereas bilateral pneumonia, cytokine storm, and pleural effusion in the variant (+) group.

Table 3

Late complications.

Late complications	Variant (–)	Variant (+)	*P* value
N	77	82	
CMV pneumonia	25	16	.023
Secondary gram (–) infection	16	38	.016
Fungal infection	8	23	.037
ARDS	27	50	.017
Cerebral/pulmonary emboli	4	13	.039
Bilateral pneumonia	20	46	.003
Pulmonary fibrosis	21	38	.048
Septic shock	15	34	.005

CMV pneumonia was more common in the variant (–) group, whereas secondary gram (–) infections, ARDS, fungal infections, cerebral/pulmonary embolism, bilateral pneumonia, pulmonary fibrosis, and septic shock were statistically significantly more common in the variant (+) group.

ARDS = acute respiratory distress syndrome, CMV = cytomegalovirus, MOF = multi–organ failure

Table 4

Therapeutic options.

Therapeutic options	Variant (–)	Variant (+)	*P* value
N	77	82	
Favipravir	62	38	<.001
Hydroxychloroquine	29	1	<.001
Azitromycin	16	0	<.001
Oseltamivir	17	0	<.001
Colchicine	18	59	<.001
Meropenem	55	37	<.001
Sulperazone	15	31	.006
Levofloxacine	53	28	<.001
Moxifloxacine	10	42	<.001
Valganciclovir	1	13	.020
Pirfenidone	0	23	<.001
Prednol-250 mg	28	46	.004
HFNC	3	40	<.001
Immune plasma	18	1	<.001
ECMO	0	**7**	<.001

Favipiravir, hydroxychloroquine (plequenil), azithromycin, oseltamivir (enfluvir), meropenem, levofloxacin (tavanic), immune plasma were more *commonly* used in the variant (–) group.
However, the use of colchicine, prednol-250 mg, sulbactam + cefoperazone (sulperazone), moxifloxacine (avelox), valganciclovir (valcyte), pirfenidone, ECMO and High Flow Nasal Cannula oxygen were *higher* in the variant (+) group.
ECMO = extracorporeal membrane oxygenator, HFNC = high frequency nasal cannula.

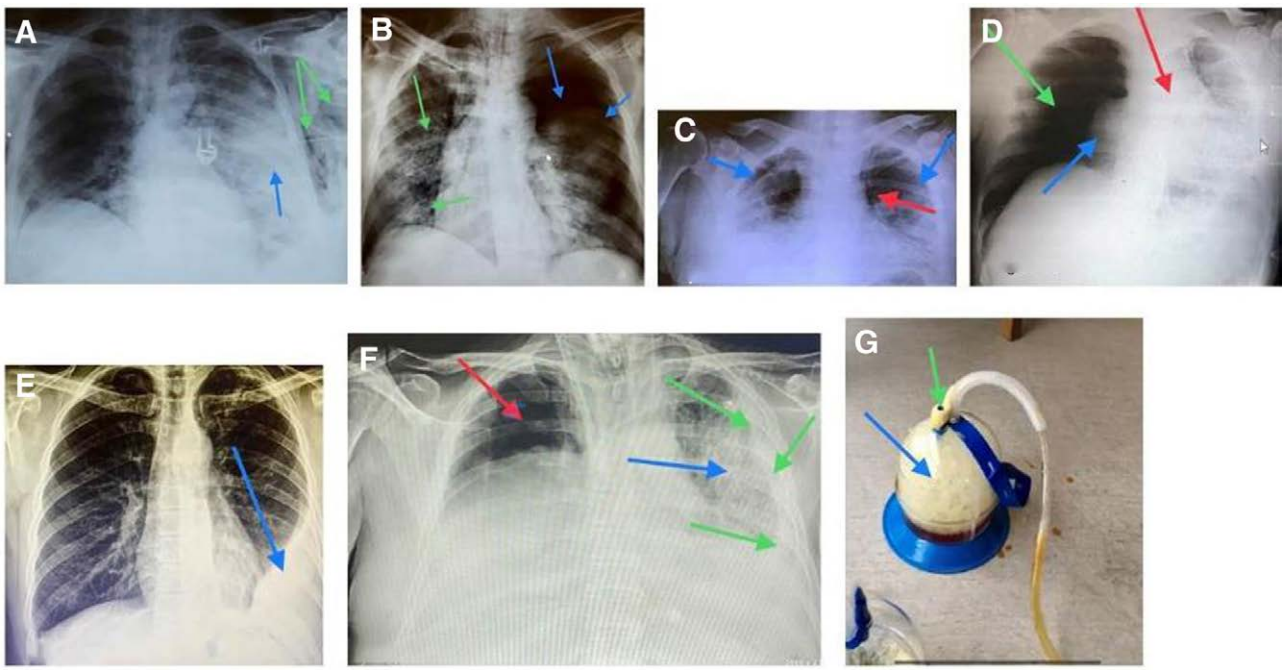

Figure 1. (PA Chest XRY images). (A) Left wide dense opacity (blue arrow) & subcutaneous emphysema (green arrows). (B) Left subtotal Pneumothorax (blue arrows) & Right middle and lower zone infiltration (green arrows). (C) Bilateral Pneumothoraces (blue arrows) with left chest tube (green arrow). (D) Right giant tension pneumothorax (green arrow) collapsing the lung (blue arrow) and shifting the mediastinum (red arrow) to the opposite side. (E) Left Hemothorax (blue arrow). (F) Right pneumothorax (red arrow) + left chylothorax (green arrows) and dense parenchymal opacity (blue arrow). (G) Massive air leakage (green arrow) and bubbles (blue arrow) in the chest tube.

variant represented just 1 in 4 new diagnoses of COVID-19, whereas by mid-December, this had increased to almost 2-thirds of the new cases in London.[7] For most of November 2020, England was in lockdown to reduce the incidence of COVID-19 cases that had steadily increased in late summer and autumn.

In the present study, we statistically analyzed our ICU experience with 159 patients with COVID–19 (77 variant negative group vs 82 variant positive group). Demographic data, symptoms, radiological findings, comorbidities, complications, and treatment options were all statistically thoroughly analyzed and presented. Our study data and treatment protocols are described in detail in the light of recent literature.

A study from England showed that 51.7% (17913) of female patients and 48.3% (16743) of male patients had the alpha variant. The alpha variant group age distribution showed that 85% of the patients were between 10 to 59 years of age.[11] Most patients were 30 to 79 years old.[12]

The median patient age ranged from 49 to 59 years.[13,14] Few cases have been reported in children younger than 15 years.

Regarding demographic data, we found that the statistically significant data were only for the male sex in the variant (–) group. While 100% of the patients were male (77 patients) in the variant (–) group, the M/F ratio (male/female) in the variant (+) group was 63/19 (76.82%).

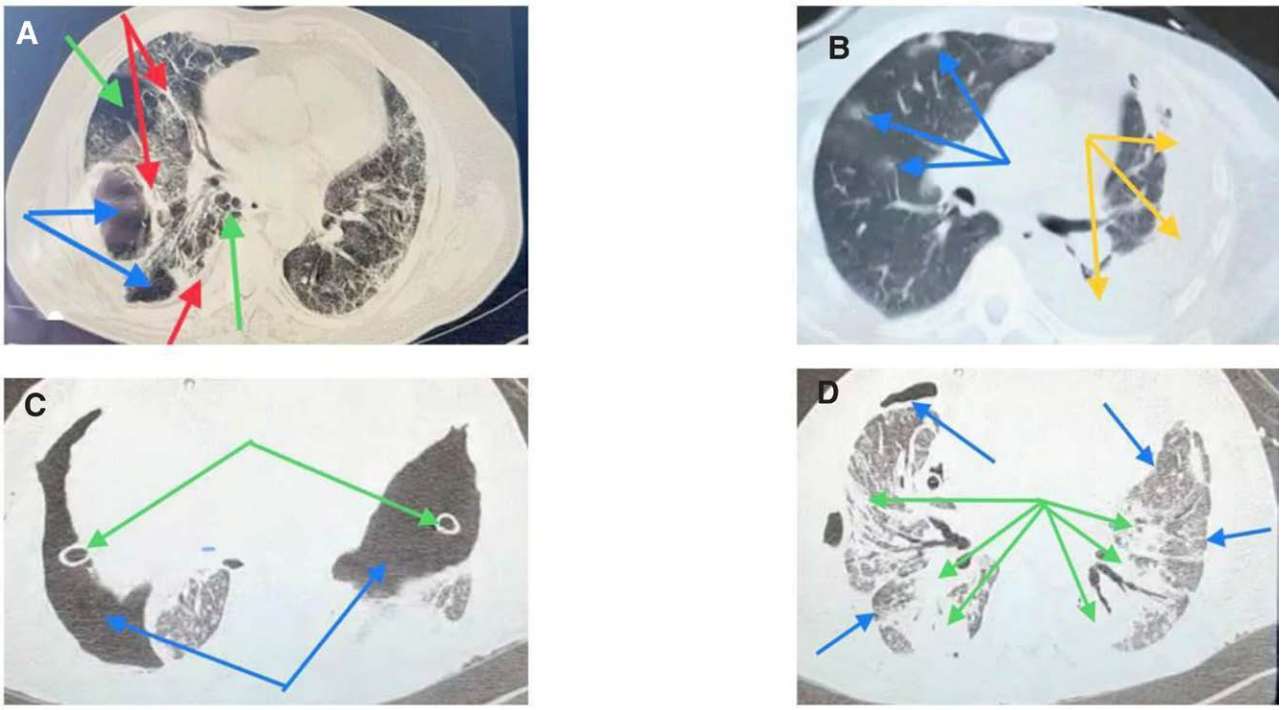

Figure 2. (Chest CT images). (A) Right cavitary (blue arrows), cystic (green arrows), and fibrotic (red arrows) parenchymas. (B) Left hemothorax (yellow arrows) + Right scaterred ground glass opacities (blue arrows). (C) Bilateral Pneumothorax (blue arrows) drained with 2 separate chest tubes (green arrows). (D) Bilateral dense thickening (blue arrows) and fibrotic stiff lung parenchyma (green arrows) a few weeks prior to death.

The median duration between symptom onset and hospitalization ranges from 3 to 10.4 days, depending on the patient's age.[15] In our series, the time from the appearance of the first symptom to hospitalization was 4 days (P = .111). The median length of hospital stay was close to 3 days in the youngest age group, but 25% of these patients stayed longer than 5.5 days (8.6) in the hospital for females. A quarter of the patients in the age group of 20 to 60 years stayed longer than 10 days, and 5% stayed longer than 24 days.

The length of stay in the ICU (based on the lognormal distribution) was on average 3.8 days for young patients, with a quarter of the patients staying longer than 7.6 days in the ICU. Similar to the length of hospital stay, the length of stay in the ICU also increases with age.[15]

In the present study, the time from hospitalization to transition to the ICU was 2 days [variant (+) vs variant (–); P < .001]. The median number of days spent in the ICU was 9 overall [10 days for variant (+) vs 6 days for variant (–); P < .001].

Particularly in the elderly and immunocompromised individuals, CoV infections may lead to severe pneumonia and subsequent patient death.[16] The mortality rates were 54.64% among severe COVID-19 cases and 5% among mild to moderate COVID-19 cases.[17] In the variant (+) group, the clinical septic picture and macrophage activating syndrome (MAS) mainly progressed simultaneously with COVID-19, probably increasing mortality rates.

In our study, 68 deaths were observed in all patient groups (N = 159), and 77 patients were intubated during this period. The mortality rates were higher in the variant (+) group, but the difference was not statistically significant. The intubation rates were 44.15% and 52.43% in the variant (–) and variant (+) groups, respectively (P = .755). The mortality rate was 50% (41 patients) in the variant (+) group and 35.06% (27 patients) in the variant (–) group (P = .156). Therefore, it seems that it can reach a significant value if the number of patients allocated increases.

Regarding comorbidities, nearly half of the patients had 1 or more coexisting medical conditions such as hypertension, diabetes, and cardiovascular disease.[13] In our study, hypertension (P = .004) and malignancy (P = .006) were more common in the variant (+) group.

Underlying immunosuppression, diabetes, and malignancy were most strongly associated with severe COVID-19 (coefficient = 53.9, 23.4, and 23.4, respectively, all P = .0007).[18] In the current study, while malignancy was not observed in the variant (–) group (0%), it was detected in 10.97% of the variant (+) group, which might indicate a negative immunocompromising effect during the clinical course.

Therefore, it can be speculated that patients with asthma are not susceptible to COVID-19. Epidemiologically, patients with asthma are less likely to suffer from COVID-19.[19] The incidence of asthma and chronic obstructive pulmonary disease was not significantly higher in the variant (+) group in our study.

Patients with SARS-CoV-2 infection usually present with fever, dry cough, upper airway congestion, sputum production, and shortness of breath but rarely with headache, hemoptysis, and diarrhea.[20,21] Loss of smell (anosmia) and taste (ageusia) has also been reported.[22] None of the patients in our study had anosmia and ageusia.

The most common symptom was fever (78.8%, 95% CI 76.2–81.3), followed by cough (53.9%, 95% CI 50.0–57.7) and malaise (37.9%; 95% CI 29.5–47.1).[18] Compared to the mild form, severe COVID-19 is associated with symptoms such as dyspnea, anorexia, fatigue, increased respiratory rate, and high systolic blood pressure.[23] Regarding clinical symptoms, the variant (+) group was shown to be significantly more symptomatic (P < .001), including fever, headache, joint and muscle pain, dyspnea, fatigue, and malaise.

Lower levels of lymphocytes and hemoglobin; elevated levels of leukocytes, AST, ALT, blood creatinine, blood urea nitrogen, high-sensitivity troponin, CK, CRP, IL 6, D-dimer, ferritin, LDH,

and procalcitonin; and a high ESR were also associated with severe COVID-19.[23]

Regarding the laboratory findings comparing both groups, only "the neutrophil count" was significantly higher in the variant (+) group ($P = .020$). Other laboratory parameters included lymphocytes ($P = .067$), ferritin ($P = .05$), D-dimer ($P = .171$), CRP, LDH, AST, ALT, urea, creatinine ($P = .320$), procalcitonin ($P = .127$), hemoglobin ($P = .972$), and hematocrit, which were not significantly different between the groups.

Many complications related to tracheostomy in patients with COVID–19 including pneumothorax, were detected in 2.3% of patients.[24] Contrary to parenchymal abnormalities, pneumothorax (1%, 95% CI: 0–3%) and pleural effusions (6%, 95% CI:1–16%) are rare.[25]

Pneumothorax ($P = 1.0$) causes air leakage dramatically seen in the video (Supplemental Digital Content [S1-Video, http://links.lww.com/MD/I565]), chylothorax ($P = .125$), hemothorax (p is no available), and ARDS ($P = 1.0$) were similar in terms of early complications in both groups, whereas pleural effusion was more common in the variant (+) group ($P = .001$).

In a study of 4012 confirmed cases of COVID-19, of which 560 (13.95%) patients with severe pneumonia were admitted. The mean age was 57.75 ± 13.96 years.[17]

In our series, the incidence of bilateral pneumonia was significantly higher in the variant (+) group (77 vs 38; $P < .001$), whereas unilateral pneumonia was more common in the variant (–) group (7 vs 0; $P = .019$).

Recently, it has been suggested that cytokine storms, particularly MAS, are involved in COVID-19 associated pneumonia and its exacerbation.[26] MAS syndrome was significantly higher in the variant (+) group in our series (52 vs 24; $P = .001$), which probably had a worse impact on survival rates.

The present autopsy-proven CMV pneumonia case highlights the potential risk of long term steroid use and the need for routine monitoring of CMV infection in critically ill patients with COVID-19.[27] COVID-19 can cause severe lymphopenia and respiratory failure, which require prolonged invasive mechanical ventilation. COVID-19 patients with severe lymphopenia or respiratory failure risk develop secondary infections. In our series, CMV pneumonia was detected in 32.46% of patients in the variant (–) group, while it was lower in the variant (+) group (19.5%) ($P = .023$).

If dyspnea continues in addition to CMV pneumonia in the clinic in immunosuppressed patients, and if we could not wean nonspecific nasal mask O_2 and continuous positive airway pressure (CPAP), we started to perform more frequent CMV diagnostic testing for the patients. Thus, early diagnosis of CMV pneumonia can be achieved. Valganciclovir, which was administered early, also allowed patients to recover faster than those who were not administered valganciclovir.

Secondary bacterial infection is a notable complication associated with worse outcomes in COVID-19 than in patients with influenza. Careful surveillance and prompt antibiotic treatment may benefit select patients. COVID-19 Patients had higher rates of bacterial infection than patients with influenza (12.6% vs 8.7%). Late infections (> 48 hours after admission) with Gram-positive bacteria are more common in COVID-19 patients (28% vs 9.5%).[28] In the current study, the rate of gram negative infections was higher in the variant (+) group (38 vs 16; $P = .016$). In addition, fungal infections (23 vs 8; $P = .037$) and bilateral pneumonia (46 vs 20; $P = .003$) were significantly increased in the variant (+) group. Most likely, these opportunistic infections arose due to the direct effect of the patients' degree of immunosuppression due to COVID–19.

Approximately 10% to 20% of patients hospitalized with COVID-19 were admitted to the ICU with severe hypoxemia and diffuse lung infiltrates; considerable progress requires mechanical ventilation for ARDS.[29] In COVID-19 disease, it is commonly observed that hypoxemia progresses to ARDS in a prolonged fashion over several days.[30] Patients with any cardiac disease were more likely to have developed ARDS (87.0 vs 40.2%) and had higher in-hospital mortality than those without (52.2 vs 5.5%, $P < .001$).[31]

In our series, in terms of late complications, ARDS rates were very high in the variant (+) group (50 vs 27; $P = .017$). Septic shock was significantly more common in the variant (+) group (34 vs 15; $P = .005$). We conclude that ARDS mainly develops in cases of coinciding bilateral pneumonia and COVID-19.

The underlying pathophysiological mechanisms of MOF in COVID-19 may be partly unique to SARS-CoV-2 (which causes viral toxicity) and is somewhat common in bacterial sepsis, such as endothelial cell damage, thromboinflammation, and dysregulated immune system activation.[32] In the present study, MOF was numerically higher in the variant (+) group (37 vs 19; $P = .092$) and mortality (41 vs 27; $P = .156$). In addition, pulmonary fibrosis was more common in the variant (+) group (38 vs 21; $P = .048$), which probably negatively affected the mortality rates.

The adjunctive therapeutic options used in the COVID-19 treatment protocol included medical drugs, HFNC, CPAP, immune plasma, plasma exchange, and ECMO.

As a treatment approach, we administered high-dose methylprednisolone for the first week with pharmacological treatment to our patients (with ARDS + bilateral pneumonia) who entered the cytokine storm. We have detected that in patients who received high-dose steroids in the first 3 days, it is important to adjust the dose according to the change in acute phase reactant levels such as ferritin and D-dimer. For example, although we administered high-dose Actemra (tocilizumab) and steroids, we could not use the immunosuppressant Actemra if sepsis and/or secondary infection was present (high procalcitonin levels).

Our treatment protocol included 3 steps, first step high-dose steroids, second step tocilizumab, third step plasma exchange and ECMO to suppress this cytokine storm. COVID-19 is an acute inflammatory disease. During treatment, we tried to prevent MAS syndrome, that is, the cytokine storm. The damage caused by COVID-19 in the lungs is directly related to cytokine storms. To prevent this, we administered 250 mg steroid pulse for the first 3 days and then 1 mg/kg steroid for 1 more week. If we detected acute phase reactant levels (generally ferritin levels were > 1000 and D-dimer increased by 4–5 times) in the first 3 days, we continued steroid treatment. However, if it did not decrease and acute phase reactants increased, we started to administer Actemra (800 mg).

Despite this treatment, if the respiratory distress did not decrease and the clinic worsened, we tried to prevent the cytokine storm by applying plasma exchange (at least 3 sessions, if necessary, 5 to 6 sessions with 24-hour intervals) as the third step of the treatment in consultation with the hematology specialist. The purpose of plasma exchange is to reduce circulating inflammatory cytokines in the blood. It is challenging to control inflammation in these organs because of the higher levels of cytokines.

Acute respiratory failure (ARF) is a major adverse event commonly encountered in severe COVID-19. Recently, HFNC has shown potential as an alternative to non-invasive ventilation in adults with ARF, including COVID-19 patients. Patients treated with HFNC showed better outcomes than those treated with non-invasive ventilation for ARF due to COVID-19.[33] In our study, we used HFNC with success and significantly more often in the variant (+) group (40 vs 3; $P < .001$). However, further studies with larger sample sizes are needed to demonstrate the benefits of HFNC in COVID-19 patients.

Convalescent plasma containing neutralizing antibodies against the SARS-CoV-2 virus was collected from the recovered patient and administered to COVID-19 patients to increase the power of the immune system or boost the patient's immune response to the virus immediately after the infection. Shen et al observed that convalescent plasma therapy improved the severe

cases of COVID-19. However, it should be stressed that based on the nature of convalescent treatment, it should be most effective in the early stages of infection before significant damage to organs.[34]

In the present study, we used immune plasma most often from patients with variant (–) (18 vs 1; $P < .001$). However, it is very likely that we used the immune plasma method in the later stages of the disease process, and could not obtain the desired effect. Therefore, we did not use this treatment for the variant (+) group.

Therapeutic plasma exchange is the process of separating and removing plasma from other components of the blood. This is considered an adjunctive treatment strategy for discarded abnormal agents to manage respiratory viral pandemics. This therapeutic potential has made plasma exchange an adjunctive treatment for managing cytokine storms and coagulopathy in respiratory viral pandemics. Plasma exchange improves organ function by clearing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins to restore hemostasis. Removal of these substances may be helpful, particularly during the early phase of sepsis.[35]

According to FDA's recent approval, plasma exchange can be used based on the guidelines recommended for investigational COVID-19 convalescent plasma.[36] The results demonstrated that the plasma exchange group had higher extubation rates than the control group ($P = .018$). Additionally, patients on plasma exchange had lower 14 days and 28 days ($P = .033$) postplasma exchange mortality rates compared to patients in the control group. Investigation of the effect of plasmapheresis in sepsis has shown that both timing and disease severity are essential for the beneficial effects of plasma exchange.[37]

In our series, we used plasmapheresis at a similar rate in both groups [variant (–) group (13 patients) vs variant (+) group (10 patients); $P = .701$]. Reducing the burden of cytokines and abnormal coagulation agents using plasmapheresis can be helpful in managing COVID-19.

CPAP has been suggested as a beneficial treatment for patients with COVID-19. CPAP treatment aims to improve oxygenation, unload respiratory muscles, and possibly delay or avoid intubation. CPAP can reduce the ICU burden if a multidisciplinary approach is implemented in a medical ward.[38]

As for the therapeutic mechanism, HFNC is supposed to generate low PEEP (3 cm H_2O on average). However, this pressure level is unstable, uncontrollable, and is affected by many factors. By contrast, nasal continuous positive airway pressure (nCPAP) can provide stable and adjustable airway pressure.[39] There remains a lack of evidence regarding the choice between HFNC and nCPAP in treating mild hypoxic respiratory failure due to COVID-19. Theoretically, the nCPAP has several advantages. In our study, we applied nCPAP as the initial treatment at a similar rate in both groups (61 vs 60; $P = 1.000$). Our clinical experience showed some superiority of nCPAP in obtaining stable airway pressure in COVID–19 patients.

4.1. ECMO

In COVID-19, refractory hypoxemia is common among critically ill patients with ARDS despite invasive mechanical ventilation, and is further complicated by respiratory and circulatory failure. This problematic situation requires the use of ECMO to assist respiration and circulation if necessary.

The WHO and NHCC have suggested using ECMO to assist respiration (and circulation, if necessary) in critically ill patients with COVID-19.[40,41] The purpose of ECMO is to resolve hypoxemia and improve blood perfusion, ultimately gaining valuable time for recovery of the cardiopulmonary system or organ transplantation.

Currently, the most frequently used modality of venovenous extracorporeal oxygenation (VV-ECMO) is to drain venous blood from the femoral vein and then infuse it back through the internal jugular vein.[42]

VV-ECMO is considered an assisting modality for reversible lung diseases with respiratory failure when traditional methods are ineffective.[43]

Much remains mysterious about 2019-CoV, and solid clinical evidence is lacking regarding the role of ECMO in rescuing critical illnesses. Despite the application of ECMO in China and recommendations on ECMO by the WHO and Chinese experts in COVID-19, several fundamental questions remain unanswered, including the benefit, timing, indications, management, and risks of ECMO, as well as global sharing of evidence from trials.[44] In our study, we used ECMO in 7 patients with no other chances of survival. Three of them were successfully weaned from ECMO and returned to their routine life after discharge. Two patients died and 1 was still on ECMO.

5. Conclusion

In this single center retrospective study, we aimed to clarify our clinical experience in detail with patients admitted to the ICU during the COVID-19 pandemic. Although some of our data did not reach statistical significance, it is clear that the results would be statistically significant if the number of patients allocated increased.

Our limitations in the current study were that we were not able to collect data of all patients admitted to the ICU because of heavy workload. Due to the imbalance of the gender distribution and low sample size in our study, it was hard to predict the real impact on the ongoing pandemic and the possible potentially more risky future variants.

It should be noted that, although the mortality and intubation rates did not differ between the groups, severe early and late complications were detected mainly in the variant (+) group, which we thought difficult to deal with. To increase the success rate and shorten the treatment time in this group, all patients should be aware of the early and late complications, diagnostic methods, and possible treatment options for the COVID-19 disease. Early diagnosis and effective treatment options may increase the treatment success rate for this new entity. Moreover, treatment should be specifically customized for each patient during the entire follow up period, day and night.

Finally, please be aware that there is much to be done to deal with future pandemics. Please note that the clinical diagnosis, behavior, and results of each COVID-19 variants that will be encountered in the future may be different.

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