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Effects of COVID-19 variation on the treatment response and disease severity in critical illness: a retrospective observational cohort study

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Abstract. – OBJECTIVE: Even though the treatment of the original variant was not fully determined, variants of COVID-19 emerged. Whether the clinic of COVID-19 has changed because of variation is controversial. The present study aimed to examine the COVID-19 severity and treatment responsiveness of critically ill patients between the original virus and emergent variations with a more comprehensive set of measures.

PATIENTS AND METHODS: Treatment responses, laboratory findings, and clinical conditions of critically ill patients with COVID-19 who were identified with variants between February 1st, and May 30th, 2021, were examined in two medical Intensive Care Units (ICUs) in tertiary care centers. Each patient received treatment in the ICU for at least one week.

RESULTS: Sixty-five (30 patients with the original variant: POV) critically ill patients were included in the study. SOFA scores, blood glucose, total bilirubin, urea-creatinine and lactate dehydrogenase levels decreased significantly in POV (*p*=.031, *p*=.002, *p*=.002, *p*=.008, and *p*=.007, respectively). Overall, patients with emergent variants (PEV) (M = 76.58, SD = 8.64) had lower partial-pressure-of-oxygen/fraction-of-inspired-oxygen ratios (P/F) than POV (M = 123.16, SD = 9.49). Use of the prone position and steroid therapy did not result in significant improvements in oxygenation of critically ill PEV. Hypertension was identified as the common comorbidity in PEV (OR=5.287).

CONCLUSIONS: We showed that the state of PEV was more severe than POV at the time of ICU admission. However, the prone position and steroids were not efficient in improving the P/F ratios. P/F ratios of PEV were significantly lower in non-invasive ventilation. These results suggest that early intubation might be necessary for PEV.

Key Words:
COVID-19, Variants of COVID-19, Critical illness, Prone position, COVID-19 severity.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), like other RNA viruses, constantly changes through mutation, with new variants emerging[1,2]. In late 2020 and early 2021, SARS-CoV-2 variants that appeared to be more transmissible than existing strains and possibly less susceptible to neutralization by host antibodies were identified in high-incidence settings[2].

The characteristics, clinical responsiveness, and outcomes of critically ill patients infected with SARS-CoV-2 variants are not yet known. Case-control studies have found no evidence for increased severity of the infection for beta (B.1.351, B.1.351.2, B.1.351.3) variation[3,4], whereas some data[5,6] suggest the SARS-CoV-2 variants might cause more severe illness. The effects of emerging variants and the original variant on intensive care unit (ICU) mortality are controversial. For instance, the Intensive Care National Audit Research Centre found no evidence of impact on the risk of hospitalization or 28-day mortality[3]. Patone et al[7] showed a 60% higher risk of 28-day mortality for the beta variation, but being infected with variants was not associated with the risk of ICU mortality at the end of critical care. In the same study, the authors reported the percentage rates of comorbidities of patients with COVID-19 with and without variants and showed that the prevalence of comorbidities was similar. Only for

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patients aged 70 years or older, the variant prevalence was lower. However, in this study, the patients examined were chosen from a community sample. How these results apply to critical illness is still not known.

In the studies discussed above, the comparisons between critically ill patients with the original variation (POV) and patients with emergent variants (PEV) for post-treatment improvements in oxygenation were not included. Their results do not fit the daily clinical observations in the ICU. Therefore, the present study aimed to obtain a better picture of the prognosis of COVID-19 in patients with SARS-CoV-2 variations using a comprehensive set of measures by comparing and contrasting the demographics and the medical characteristics of severity and treatment responsiveness.

Accordingly, we first assessed the differences in laboratory findings, scoring systems, and clinical responsiveness for COVID-19 treatments in POV and PEV. We aim to predict disease severity and examine the comorbidities and characteristics of positive tests for PEV in critical illness. Furthermore, we compared the frequency of use of respiratory support systems in POV and PEV and assessed the differences in P/F and PCO_2 rates measured at specific time intervals. Finally, we explored the risk of mortality in critically ill POV with COVID-19 compared with emerged variants.

Patients and Methods

Study Design

Bursa City Hospital Ethical Committee approved this multicenter retrospective observational cohort study (no: 2021-7/7). Data were collected in two hospitals for patients who met the criteria on the relevant dates. Our study was conducted retrospectively, informed consent was obtained from all patients/patient relatives during admission to intensive-care-unit that the results of clinical status, laboratory and radiological examinations can be used for scientific publications without specifying the descriptive characteristics (name, surname, ID number) of the patients.

Inclusion and Exclusion Criteria

We included adult patients admitted to any of the adult ICUs at our facility with laboratory-confirmed COVID-19 polymerase chain reaction (PCR)-positive specimens and also cycle threshold (Ct) values of ≤ 35 between February 1st and May 30th, 2021, in the study. Specimens that were not positive for mutation (N501Y: VOC 2020 12/01 or B.1.1.7, B.1.351, P.1, B.1.525, and B.1.526) were defined as POV, and specimens that were positive for mutations were defined as PEV. Individuals were excluded if they were (1) discharged from the ICU or died before one week or (2) had liver or renal failure unrelated to COVID-19.

Variant Virus Detection Protocol

Results for multiplex reverse transcriptase (RT)-PCR assays together with positive and negative results for the other targets are shown in Table I.

Data Collection

We recorded the demographics of patients, their comorbidities, acute physiology and chronic health evaluation (APACHE II) scores, sequential organ failure assessment (SOFA) scores (SOFA score was calculated using the worst values observed within 72 hours after ICU admission), whether patients remained in the prone position, corticosteroid treatments (none, dexamethasone, prednisolone, and pulse steroid), hospital stay (days) [length of stay in hospital until admission to intensive care unit (ICU)]. Also, laboratory test results on admission to the ICU [blood glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatine, lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), procalcitonin, D-dimer], partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2:P/F) ratios (initial (P/F_1), after three days (P/F_3) and one week (P/F_7), initial partial arterial carbon dioxide pressures ($PaCO2_1$), after three days ($PaCO2_3$) and after one week ($PaCO2_7$), respiratory support [invasive mechanical ventilation (IMV), noninvasive ventilation (NIMV) and conventional oxygen therapies (COT)] and outcome (28-day mortality) were recorded.

Results

Statistical Analysis

Data analysis was conducted using the SPSS statistical software (SPSS Inc. 26.0: IBM, Armonk, NY, USA) and *p*-values of <.05 were considered statistically significant.

Table I. Detection of variant viruses protocol.

Situation	FAM	ROX	CY5	Result
1	_	_	_	1) Negative for SARS-COV-2
2	+	_	_	1) Positive for SARS-COV-2 2) Negative for B.1.1.7, B.1.351, P.1, B.1.525 and B.1.526
3	+	+	+	1) Positive for SARS-COV-2 2) Positive for B.1.1.7 (VOC-202012/01) that carrying N501Y 3) Negative for B.1.351, P.1, B.1.525 and B.1.526
4	+	+	_	1) Positive for SARS-COV-2 2) Positive for B.1.351, P.1, B.1.525 or B.1.526 3) Negative for B.1.1.7 (VOC-202012/01) that carrying N501Y
5	+	_	+	1) Positive for SARS-COV-2 2) Positive for B.1.1.7 that not carrying N501Y 3) Negative for B.1.351, P.1, B.1.525, B.1.526 and B.1.1.7 (VOC-202012/01) that carrying N501Y

Abbrevations: FAM; Fluorescence channel that internal control probe is labeled with FAM, ROX; Fluorescence channel that internal control probe is labeled with ROX, CY5; Fluorescence channel that internal control probe is labeled with CY5.

Patient Population and Characteristics

We screened 45,997 samples of SARS-CoV-2 in two hospitals between February 1st and May 30th, 2021. Among 7952 positive results, 5891 were screened for COVID-19 variants and variant analyses of 4363 patients were positive. However, only 48 of 4363 patients and 39 variation-negative patients with COVID-19 were taken to the adult ICUs in the two hospitals. The treatments of 35 patients who were variation-positive and 30 who were variation-negative (Figure 1) who were admitted to the ICU continued for at least one week. The characteristics of patients according to the groups can be seen in Table II.

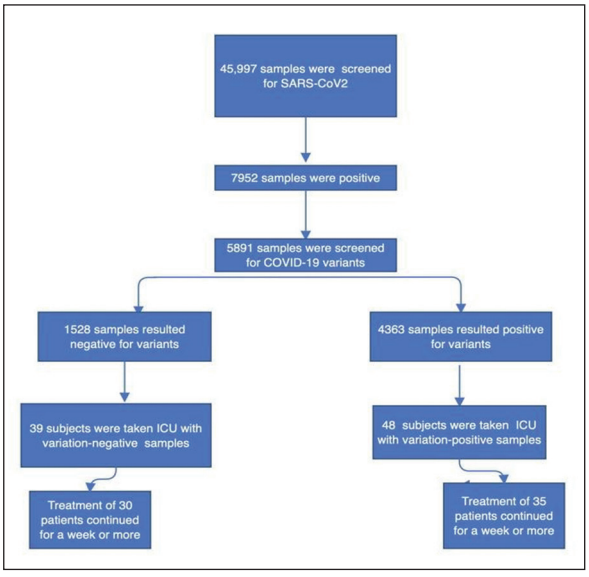

Figure 1. Flow chart.

Disease Severity

Differences in Laboratory Findings and Scoring Systems in POV and PEV

SOFA scores ($U = 368.00$, $p = .031$), blood glucose levels ($U = 289.50$, $p = .002$), total bilirubin levels ($U=284.50$, $p = .002$) urea-creatinine levels ($U=325.00$, $p = .008$; and $U=319.50$, $p = .007$, respectively) and LDH levels ($U=256.50$, $p<0.001$) were significantly higher in PEV compared with POV. We found no significant differences between POV and PEV according to acute-phase reactants, D-dimer, ferritin, procalcitonin, and CRP levels ($p > .422$ for all).

Clinical Responsiveness for COVID-19 Treatments in POV and PEV

Prone Position

Out of 65 patients, 31 were placed in the prone position two or more times per day. Fifty-four percent of the patients in the prone position were PEV. A 3×2×2 mixed-design analysis of variance (ANOVA) was conducted to explore the effects of time, PEV, and prone position on P/F scores. The results showed a significant

Table II. Medical and demographic characteristics of patients.

	PEV (n: 35) (mean ± SD)	POV (n: 30) (mean ± SD)	*p*
Age	70.29 ± 12.25	65.57 ± 11.99	.12
Hospital day	8.20 ± 7.32	6.97 ± 6.67	.48
APACHEII	14.31 ± 1.24	14.27 ± 7.39	.32
SOFA	4.77 ± 1.93	3.67 ± 1.24	.03
P/F_1	69.85 ± 31.81	80.32 ± 62.74	.10
P/F_3	77.48 ± 44.24	130.41 ± 67.39	< 001
P/F_7	85.16 ± 51.05	155.75 ± 80.79	< 001
$PCO2_1$	40.94 ± 11.50	39.50 ± 11.57	.37
$PCO2_3$	40.07 ± 8.60	39.05 ± 11.43	.40
$PCO2_7$	40.02 ± 9.96	44.96 ± 9.00	.64
Blood glucose	248.80 ± 105.67	186.50 ± 81.66	.002
Bilurubine	0.63 ± 0.27	0.44 ± 0.29	.002
AST	52.31 ± 13.32	32.27 ± 18.37	.71
ALT	34.66 ± 21.66	35.53 ± 40.17	.20
Urea	83.70 ± 51.78	55.18 ± 28.60	.008
Creatine	1.52 ± 1.61	0.98 ± 0.89	.007
D'dimer	3.75 ± 7.15	3.22±3.69	.42
LDH	624.54 ± 321.78	412.07 ± 172.90	< 001
Ferritin	850.91 ± 482.99	855.28 ± 751.49	.50
Procalcitonin	0.58 ± 0.86	2.60 ± 11.15	.52
CRP	121.89 ± 71.20	128.40 ± 67.53	.57

Abbrevations: PEV; patients with emergent variants, POV; patients with original variant, APACHEII; acute physiology and chronic health evaluation, SOFA; sequential organ failure assessment; hospital day; lenght of stay in hospital until admission to intensive care unit (ICU), P/F_1; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured at the admission to the ICU, P/F_3; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured on the 3rd day of ICU admission, P/F_7; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured on the 7th day of ICU admission; $PCO2_1$; partial arterial pressure of carbon dioxide measured at the admission to the ICU, $PCO2_3$; partial arterial pressure of carbon dioxide measured on the 3rd day of ICU admission, $PCO2_7$; partial arterial pressure of carbon dioxide measured on the 7th day of ICU admission, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, CRP; C-reactive protein.

main effect for time, F (2. 122) = 31.32, p < .001, h_p^2 = 34, MSe = 1098.45. Pairwise comparisons with LSD corrections showed that P/F scores significantly increased from day 1 (M = 74.88, SD = 6.12) to day 3 (M = 103.57, SD = 7.05), and day 7 (M = 121.18, SD = 8.44) (p < .001 for all).

There was also a main effect of PEV, F (1.61) = 13.18, p =.001, h_p^2 =.18, MSe = 7778.45. Overall, PEV (M = 76.58, SD = 8.64) had lower P/F than POV (M = 123.16, SD = 9.49). There was also a significant interaction between time and PEV, F (2. 122) = 14.05, p < .001, h_p^2 =.19, MSe = 1098.45. There was a significant increase from day 1 to day 7 for POV (p < .001 for all), whereas for PEVs, P/F values did not change (p >.107 for all).

Contrary to our expectations, there was no effect of the prone position (p = .227). The interactions between the prone position and PEV, prone position and time, and the three-way interaction were also not significant (p > .373 for all; Figure 2).

Steroid Treatments

A 3×2×3 mixed-design ANOVA was conducted to explore the effects of time, PEV, and steroid treatment type on P/F scores and the interactions

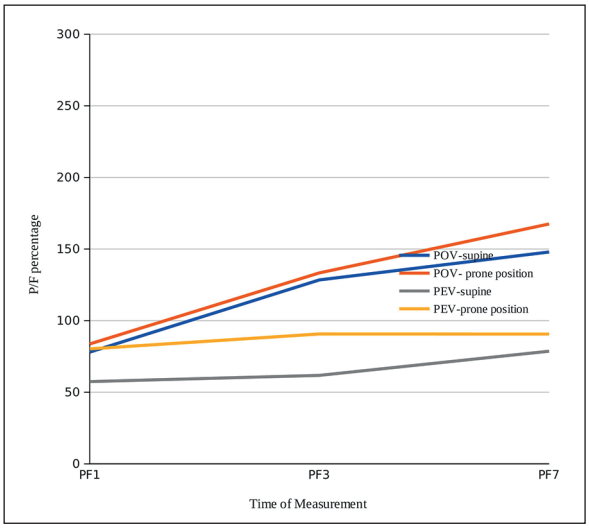

Figure 2. Prone position and P/F ratios.

amongst these variables. The main effects of time and PEV and the interaction between time and PEV were significant, as stated above. However, there was no main effect of steroid treatment type, and the interactions between steroid type, time, and PEV, and the three-way interaction was not significant ($p > .125$ for all, Figure 3).

Comorbidities and Characteristics of Positive Tests for Variation in Critical Illness

We identified hypertension as the only common comorbidity in PEV. Hypertension in critically ill patients was associated with a significantly increased risk for being PEV (*OR*=5.287; 95% CI: [1.481-18.872]; $p = 0.01$). However, age, sex, diabetes mellitus, and congestive heart failure or coronary artery disease were not associated with an increased risk for being PEV ($p > .110$ for all).

Percentage of Use for Respiratory Support Systems

Invasive ventilation was performed on 30 (46.2%) patients in total. Among them, 16 were POV and 14 were PEV. Non-invasive ventilation and high-flow nasal oxygen therapy were administered to 24 patients. Eleven patients received conventional oxygen therapy. We found no significant differences between POV and PEV according to respiratory support system use ($p = .320$).

Serial PCO_2 Ratios

There was no significant difference between POV and PEV in critical illness for PCO_2 levels on ICU admission, and on the 3rd and 7th day after ICU admission ($p > .125$ for all).

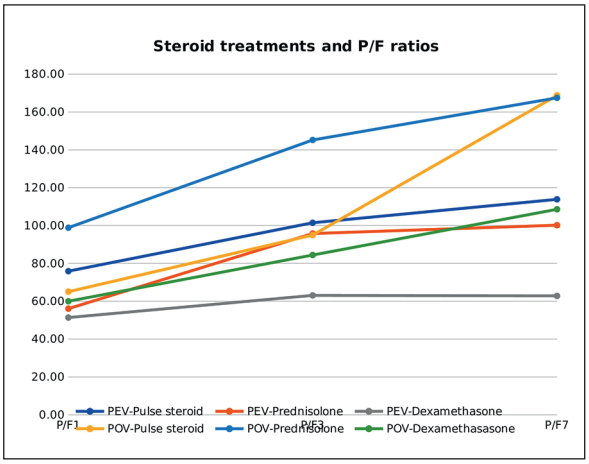

Figure 3. Steroid treatmens and P/F ratios.

28-day Mortality and Affecting Factors

Higher total bilirubin and creatinine levels during admission to the ICU were associated with an increased risk of 28-day mortality (*OR*=89.13, 95% CI: [2.00-3960.22]; $p = .02$) and (*OR*=3.47, 95% CI: [1.134-10.6]; $p = .029$), respectively. It was also found that patients using dexamethasone had lower 28-day mortality (*OR*=0.026, 95% CI: [0.002-0.391]; $p = .008$). No significant difference was found between POV and PEV for 28-day mortality (95% CI: [0.67-6.635]; $p = .73$; Table III).

Discussion

COVID-19 caused larger numbers of patients to receive critical care than we have seen before. Up to May 2020, worldwide mortality following critical illness with COVID-19 was reported as 40-50 %[8]. Even though the treatment of the original virus was not yet fully determined, variants of COVID-19 emerged. However, there are very few articles on these new variants, and they were only concerned with mortality and ICU admission rates[5-7]. To our knowledge, this is the first study to investigate whether the severity of COVID-19 increased due to variations through laboratory parameters, scoring systems, responses to treatments, P/F indexes, respiratory supports, and differences in 28-day mortality. We found that 28-day mortality was not different in critically ill patients with COVID-19 with and without variants, despite the increase in disease severity.

We found that the SOFA score, LDH, and blood glucose levels were higher in PEV. This suggests a relation between these variables and the severity of the disease. SOFA scores can be used to determine the level of organ dysfunction and mortality risk in patients in the ICU[9]. A recent article[10] suggested that SOFA scores did not predict COVID-19 mortality. Furthermore, in recent studies, LDH[11] and high blood glucose levels[12] were associated with mortality in critically ill patients. Therefore, in the present study, we also used LDH and high blood glucose levels to assess disease severity. To our knowledge, this is the first study to examine these parameters and their relation to disease severity and mortality probability. We showed that PEV had higher disease severity and probability of mortality when compared with the original virus in the ICU.

Table III. 28-day mortality and affecting factors.

Independent variables	B	SE	Sig.	OR	95% CI Lower	Upper
Gender	.081	1.018	.937	1.084	.147	7.976
Age	.035	.043	.411	1.036	.952	1.127
P/F_1	-.021	.020	.308	.980	.942	1.019
P/F_3	.023	.015	.122	1.023	.994	1.054
P/F_7	-.009	.011	.408	.991	.969	1.013
PEV	-.409	1.174	.728	.664	.067	6.635
DDimer	-.038	.124	.755	.962	.755	1.226
CRP	-.001	.008	.862	.999	.984	1.014
LDH	.003	.003	.263	1.003	.997	1.009
DM	-.036	1.077	.494	2.090	.253	17.264
HT	-.052	1.048	.973	.965	.124	7.517
$Respsup_1$	-.351	2.154	.870	.704	.010	48.003
$Resp.sup_2$	1.233	1.495	.410	3.432	.183	64.311
Proneposition	-1.922	1.634	.239	.146	.006	3.599
Dexametazone	-3.647	6.975	.008	.026	.002	.391
Metilprednizolon	-.613	.350	.554	.542	.071	4.125
Hostday	-.128	3.053	.081	.880	.762	1.016
Totalbilirubin	4.490	5.381	.020	89.133	2.006	3960.215
AST	.010	.129	.719	1.010	.957	1.066
ALT	.002	.019	.901	1.002	.966	1.040
Ure	-.032	.016	.047	.968	.938	1.000
Creatine	1.244	.570	.029	3.468	1.134	10.608
Ferritin	.000	.001	.926	1.000	.998	1.002
Procalcitonin	.032	.069	.645	1.032	.902	1.181

Abbrevations: P/F1; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured at the admission to the ICU, P/F_3; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured on the 3rd day of ICU admission, P/F_7; partial-pressure-of-oxygen/fraction-of-inspired-oxygen (PaO_2/FiO_2) measured on the 7th day of ICU admission, PEV; patients with emergent variants, CRP; C-reactive protein, LDH; lactate dehydrogenase, DM; Diabetes mellitus, HT; hypertension, $Respsup_1$; Non-invasive ventilation, high-flow nasal oxygen therapy and conventional oxygen therapy, $Resp.sup_2$; invasive ventilation Hostday; lenght of stay in hospital until admission to intensive care unit (ICU), AST; aspartate aminotransferase, ALT; alanine aminotransferase.

Since the beginning of the pandemic, COVID-19 treatment guidelines[13] have been established and critically ill patients have been treated accordingly. However, we do not know whether the treatment response of COVID-19 has changed due to the variants. In the present study, we compared the responses of POV and PEV to the prone position and steroid treatments, two treatment methods recommended in these guidelines for their effectiveness in improving oxygenation. Although many publications regarding patients with COVID-19 found that the prone position improved oxygenation[14,15], we observed that there was no significant increase in P/F ratios on the 3rd and 7th days compared with ICU admission of PEV who were placed in the prone position. Although corticosteroids have received worldwide attention as a potentially effective treatment for COVID-19[16], we found no difference in the improvement of oxygenation as a result of different corticosteroid treatments in POV and PEV. This unresponsiveness to these treatments may suggest an increase in the severity of the disease and a need for different treatment options.

Patone et al[7] examined the percentage rates of comorbidities of PEV and POV with COVID-19 in a very large population and they found that PEV and POV were similar to each other in terms of comorbidities and sample characteristics. Similarly, we observed no significant associations between age, sex, congestive heart failure or coronary artery disease, and increased risk for PEV. Also, for patients with diabetes, blood glucose levels were not related to an increased risk of PEV. However, in our study, the prevalence of hypertension was higher in PEV. Even though hypertension has been identified as one of the most common comorbidities and a risk factor for severe disease and adverse outcomes in patients with COVID-19[17], there was no evidence that patients with hypertension with COVID-19 were more likely to be PEV. This is the first study to show any differences between

POV and PEV in hypertension prevalence. However, it should be noted that Patone et al[7] used a community sample, whereas our patients were in the ICU, suggesting that having hypertension before PEV diagnosis might make admission to the ICU more likely.

In a previous study[7] conducted in the United Kingdom, only the percentage rates of P/F rates of variants of concern (VOC) and non-VOC patients on the first day of intensive care treatment were given without statistical analysis. In our study, we compared ICU admission and P/F rates on the 3rd day and 7th day. Although no significant difference was found between POV and PEV in critically ill patients when compared according to P/F ratios on ICU admission, measurements of these rates on the 3rd and 7th day after ICU admission were significantly lower in PEV. However, remarkably, at the end of the first week after ICU admission, the number of patients managed with invasive and non-invasive ventilation was not different between the two groups; one would expect higher rates for the PEV group due to lower P/F ratios. In our opinion, an earlier transition to invasive mechanical ventilation is required in critically ill PEV.

Similar to the findings from other studies[4-7], our analyses indicated no significant difference in COVID-19 28-day mortality risk for PEV compared with those in the POV group.

A limitation of this study was that the data collection took place in two different centers in two different cities. This led to very different ICU admission rates between critically ill POV and PEV. Accordingly, we could not accurately compare the risk of critical care admission in the community between the two groups. Future studies should employ single data collection centers or centers that are more similar to each other in terms of patient characteristics. Furthermore, the limited time duration dedicated to data collection due to the governmental regulations and the exclusion/inclusion criteria resulted in a smaller sample size than intended. Future studies using larger sample sizes may shed more light on the situation.

Conclusions

These findings suggest that COVID-19 may have become more unresponsive to treatment, especially in critically ill patients. However, P/F ratios of PEV were always lower than in POV. We believe that invasive mechanical ventilation should be considered earlier than for COVID-19 POV to improve oxygenation in patients with COVID-19 with emerged variants.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

Bursa City Hospital Ethical Committee approved this multicenter retrospective observational cohort study (no: 2021-7/7).

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