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The effect of using iloprost on prognosis in COVID-19 patients with ARDS: a retrospective clinical study

R. SARI KÜÇÜK[1], K. ULUÇ[1], Ş. MERVE ÇOLAKOĞLU[1], C. KILINÇ BERKTAŞ[2], S. MUTLU[1], N. TURGUT[1]

[1]Department of Intensive Care, Prof. Dr. Cemil Taşcıoğlu City Hospital, Turkey, Istanbul
[2]Department of Intensive Care, Başakşehir Çam and Sakura City Hospital, Turkey, Istanbul

Abstract. – OBJECTIVE: Epithelial damage together with endothelitis and microvascular thrombi are responsible for COVID-19 associated acute respiratory distress syndrome (ARDS). Iloprost, improves endothelial damage and reduces thrombotic complications with its vasodilator, anti-platelet, anti-inflammatory, and anti-fibrotic effects. In our study, we aimed to determine the effect of iloprost on oxygenation, hemodynamics, weaning, and mortality in severe COVID-19 ARDS.

PATIENTS AND METHODS: This was a retrospective study conducted in a pandemic hospital in the city of Istanbul, Turkey. Patients, with severe COVID-19 ARDS, who were receiving iloprost for seven days were included in the study. The demographic data, APACHE II, and SOFA (Sequential Organ Failure Assessment score) scores (at admission and discharge), pH, PaO_2, PCO_2, $SatO_2$, lactate, PaO_2/FiO_2 (inspiratory fractionated oxygen), respiratory rate-oxygenation (ROX) index (peripheral oxygen saturation/fraction of inhaled oxygen), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressures (MAP), heart rate (HR) values were recorded before starting iloprost (T0), and on days of iloprost administration (2.0 nanograms/kg/minute/6 hours/day) (T1, T2, T3, T4, T5, T6, T7), and the day after last day of iloprost administration (T_{final}). Also, mortality was recorded in a retrospective manner. Two groups were formed according to mortality (Group M) and discharge (Group D).

RESULTS: A total of 22 patients (16 men, 6 women) were evaluated. Age, APACHE II, SOFA scores were higher in Group M. The lactate value at T1-3-4-5-7 was lower than T0 in both groups. PaO_2 value between T2-T_{final} was higher than T0. A statistically significant increase was found in PaO_2/FiO_2 levels in both groups. The PaO_2/FiO_2value between T5-T_{final} was significantly lower in Group M compared to Group D. ROX index was significantly higher between T4-T_{final} when compared with T0.

CONCLUSIONS: Iloprost improves oxygenation but has no effect on mortality in COVID-19 ARDS.

Key Words:
ARDS, COVID-19, Iloprost.

Introduction

SARS-CoV-2, which is the biological agent responsible for COVID-19, causes inflammation in various tissues by binding to the angiotensin-converting enzyme (ACE2) receptors, which are commonly found in the body. ACE2 receptors, which are located on endothelial cells and cardiac podocytes, are direct targets for SARS-CoV-2 in the endothelium. After the examination of the pulmonary vascular bed, it was determined that the virus causes thrombosis, microangiopathy, endothelial activation, and angiogenesis in COVID-19 patients[1,2]. Microvascular thrombi are responsible for disease severity and ventilation-perfusion deficit.

In severe COVID-19 patients, it was determined that lymphocytes, CD4+T, and CD8+T cells were decreased, while neutrophils increased in the blood. The observation of interstitial mononuclear cell infiltration led by lymphocytes in the lungs in postmortem examinations may explain lymphopenia. At the same time, leukocyte accumulation and inflammatory endothelial damage occur as a result of transcriptional activation induced by proinflammatory mediators released during the cytokine storm syndrome that occurs in COVID-19 patients. As a result of endothelial damage, vascular permeability increases, and damage occurs in the affected organ[3].

Iloprost is a long-acting prostaglandin I2 (PGI2) analog. PGI2 is a product of the cyclooxygenase 2 (COX-2) enzyme system produced in endothelial cells, and it regulates microvascular circulation with effects such as vasodilation, reduction of microvascular permeability, reduction

Corresponding Author: Rabia Sari Küçük, MD; e-mail: drrabiasari@yahoo.com

of platelet aggregation, leukocyte activation, and chemotaxis[4]. It has been shown[5] to reduce oxidative stress in endothelial cells and protect from endothelial damage by inhibiting collagen synthesis. It also reduces leukocyte and platelet aggregation, which is important in the development of acute respiratory distress syndrome (ARDS) in the lungs[6].

The benefits of iloprost, which is clinically approved for use by inhalation in pulmonary arterial hypertension, have been demonstrated[7-9] in clinical conditions such as ischemia-reperfusion injury, extremity ischemia, and systemic siclerosis.

In this study, we aimed to investigate the effect of iloprost, which has positive effects on the endothelium and therefore microcirculation in different diseases, as well as on oxygenation, hemodynamics, weaning, length of stay in the intensive care unit, and mortality in COVID-19 patients who were followed-up with severe ARDS.

Patients and Methods

After the local Ethics Committee approval was obtained for the study (09.02.2021/ E- 48670771-514.10), patients with a probable/definite diagnosis of COVID-19 who were admitted to the University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital's 3rd level Intensive Care Unit between 18.03.2020-31.12.2020 were included. The study was conducted in accordance with the conditions recommended by the Helsinki Declaration and the European Union Council directives (ETS 123; 86/609/EEC), and informed consent was obtained from the relatives, or the patients included in the study. This work was not financially supported.

Inclusion Criteria

Patients who developed severe COVID-19 ARDS[10], ≥18 age, PaO_2/FiO_2 ≤150, patients without indication for extracorporeal membrane oxygenation, patients receiving iloprost 2.0 nanograms/kg/minute/6 hours/day for a duration of 7 days. Patients without a diagnosis of COVID-19 were excluded from the study.

Patients' demographic data, comorbidities, time to Intensive Care Unit admission, APACHE II and SOFA (sequential organ failure assessment score) scores at admission and discharge, iloprost onset day, duration of iloprost administration, duration of non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV) and high flow nasal oxygen (HFNO) application, length of stay in the Intensive Care Unit, and mortality were recorded, retrospectively. The levels of pH, PaO_2, $PaCO_2$, $SatO_2$, and lactate from arterial blood gas (ABG) samples, partial arterial oxygen to fractionated oxygen ratio (PaO_2/FiO_2), respiratory rate-oxygenation (ROX) index [peripheral oxygen saturation/inhaled oxygen fraction ratio (SpO_2/FiO_2)/RR (respiratory rate)] in patients administered HFNO, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR) were recorded as T0, T1, T2, T3, T4, T5, T6, T7, T_{final}. T0-T_{final} was defined as:

T0: before starting iloprost.

At the end of the iloprost infusion for T1-T7:

T1: first day of iloprost administration;

T2: second day of iloprost administration;

T3: third day of iloprost administration;

T4: fourth day of iloprost administration;

T5: fifth day of iloprost administration;

T6: sixth day of iloprost administration;

T7: seventh day of iloprost administration;

T_{final}: the day after the end of treatment.

According to mortality, 2 groups (Mortality: Group M, Discharge: Group D) were formed.

Definition of Severe Respiratory Infection (Pneumonia)[10]

In the patient with fever and respiratory tract infection findings:

- Respiratory rate >30/min and/or
- Severe respiratory distress (dyspnea, use of extra respiratory muscle) and/or
- Oxygen saturation <90% at room air (PaO_2/FiO_2 <300 in the patient receiving oxygen).

Statistical Analysis

SPSS 15.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. In descriptive statistics, numbers and percentages were used for categorical variables, while medians and interquartile ranges were used for numeric variables. The rates in independent groups were compared with the Chi-Square test. The comparisons of two independent groups were made with the student *t*-test when the numerical variables met the normal distribution condition, and with the Mann-Whitney U-test when the condition was not met. The differences in numerical variables in dependent group analyses were analyzed with Repeated Measurement Analysis of Variance when the data was normally distributed and with the Friedman test for un-normal distribution. The subgroup analyses were performed with Wilcoxon analysis in a nonparametric test

and interpreted with Bonferroni correction. The relationships between numerical variables were analyzed using Pearson's Correlation analysis if the parametric test condition was met, and Spearman's Correlation analysis if the condition was not met. The statistical significance level was accepted as p-values <0.05.

Results

A total of 22 patients were included in the study (16 men, and 6 women). While comorbidities were not different between the two groups, age, APACHE II, and SOFA scores were significantly higher in Group M (n=13) compared with Group D (n=9) (p=0.028, p=0.002, p=0.009, respectively). SARS-CoV-2 PCR antigens of all patients were positive. There was no significant difference between the two groups in terms of co-morbidity, the service where the patient was hospitalized before the ICU, time to the hospitalization in the ICU, date of start of iloprost therapy, the duration of iloprost administration, the duration of HFNO administration, the duration of IMV, the duration of ICU stays, and the duration of stay on the ventilator (Table I).

When all the patients were evaluated, the lactate levels of patients after iloprost administration at T1-3-4-5-7 were found to be statistically significantly lower than the lactate level before treatment (p=0.042, p=0.042, p=0.037, p=0.045, p=0.042) (Figure 1).

The level of lactate of Group M at T0, T5, T6, and T_{final} was higher than Group D (p=0.012, p=0.049, p=0.004, p=0.004) (Table II).

As the patient's age increased, baseline lactate levels remained significantly higher (p=0.036). In patients with high APACHE II scores, lactate levels at T0-5-6-T_{final} were significantly higher (p=0.035, p=0.041, p=0.007, p=0.005). In patients with a high baseline SOFA score, the T0 lactate level was found to be significantly high (p=0.007). There was no statistically significant effect observed regarding the lactate values at admission to the hospital and days of iloprost administration on the duration of HFNO treatment, duration of IMV, length of stay in the ICU, and duration of ventilator treatment.

When patients were evaluated without grouping, the mean pH values at T7 and T_{final} were statistically significantly lower than the mean pH value before the treatment (T0) (p=0.018, p=0.009). When the groups were compared, the mean pH values of the patients at T7 and T_{final} in Group M were significantly lower than those in Group D (p<0.001) (Table III).

In all patients, the change in $PaCO_2$ levels during ICU follow-up was statistically significantly higher starting from T2 when compared to T0 (p=0.010, p=0.014, p=0.004, p<0.001, p=0.002, p<0.001, p=0.001, respectively). The change in $PaCO_2$ levels in both groups was statistically significant (p=0.004, p=0.001). The mean $PaCO_2$ values from T3 were statistically significantly

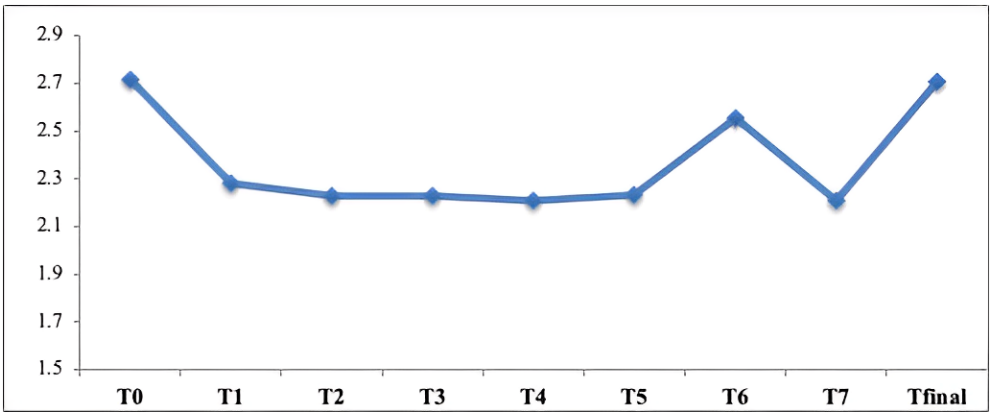

Figure 1. The changes in lactate levels of patients after iloprost. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7. T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

Table I. The demographic data of patients.

		Final status Total	Discharge (Group D) n=9 (40.9%)	Exitus (Group M) n=13 (59.1%)	*p*-value
Gender n (%)	Male	16 (72.7%)	6 (66.7%)	10 (76.9%)	0.655
	Female	6 (27.3%)	3 (33.3%)	3 (23.1%)	
Age Mean±SD		63.0±12.6	56.1±13.4	67.8±9.8	0.028*
Comorbidity n (%)	No	6 (27.3%)	6 (27.3%)	3 (23.1%)	0.655
	Yes	16 (72.7%)	16 (72.7%)	10 (76.9%)	
	DM	9 (40.9%)	9 (40.9%)	7 (53.8%)	0.203
	Hypertension	12 (54.5%)	12 (54.5%)	7 (53.8%)	1.000
	COPD	3 (13.6%)	3 (13.6%)	2 (15.4%)	1.000
	IHD	8 (36.4%)	8 (36.4%)	5 (38.5%)	1.000
	CVD	3 (13.6%)	3 (13.6%)	3 (23.1%)	0.240
	PE	1 (4.5%)	1 (4.5%)	0 (0.0%)	0.409
	Breast Canser	1 (4.5%)	1 (4.5%)	1 (7.7%)	1.000
	Alzheimer	1 (4.5%)	1 (4.5%)	0 (0.0%)	0.409
Hospitalization before ICU n (%)	Emergency	10 (45.5%)	10 (45.5%)	4 (30.8%)	0.192
	Pandemic Service	12 (54.5%)	12 (54.5%)	9 (69.2%)	
Admission duration to ICU/day		1.91±2.39	1.00±1.41	2.54±2.76	0.154
APACHE II		29.0±9.3	22.2±7.7	33.7±7.4	0.002*
SOFA Mean±SD		7.82±2.68	6.11±1.62	9.00±2.68	0.009*
SARS-CoV-2 PCR	Positive n (%)	22 (100%)			
Ilioprost start day Mean±SD		2.36±1.22	1.89±0.78	2.69±1.38	0.150
Ilioprost administration duration/day Mean±SD		8.05±1.59	8.11±1.69	8.00±1.58	0.876
HFNO duration/day Mean±SD		7.3±7.2	10.2±8.6	4.4±4.1	0.154
IMV duration/day Mean±SD		12.9±6.0	11.6±6.0	13.4±6.2	0.586
ICU hospitalization duration/day Mean±SD		17.0±7.1	17.6±7.7	16.7±6.9	0.786
Length of stay on the ventilator/day Mean±SD		13.6±6.6	11.6±6.0	14.4±6.9	0.439

DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, IHD: Ischemic heart disease, CVD: Cerebrovascular disease, PE: Pulmonary embolism, HFNO: High flow nasal oxygenation, IMV: Invasive mechanical ventilator, ICU: Intensive care unit, SD: Standard deviation. *: Statistically significant difference.

Table II. Lactate levels of discharged and exitus patients.

	Final status Discharge (Group D) Mean±SD	Exitus (Group M) Mean±SD	*p*-value
Lactate T0, mmol/L	2.10±0.75	3.14±0.95	0.012*
Lactate T1	2.02±0.74	2.46±0.69	0.170
Lactate T2	2.29±0.49	2.19±0.97	0.782
Lactate T3	2.16±0.56	2.28±0.78	0.679
Lactate T4	1.98±0.51	2.36±0.78	0.216
Lactate T5	1.86±0.43	2.49±0.80	0.049
Lactate T6	1.97±0.63	2.96±0.76	0.004*
Lactate T7	1.83±0.52	2.47±0.96	0.086
Lactate T_{final}	1.71±0.55	3.40±2.18	0.004
p*	0.278	0.088	

T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment. SD: Standard deviation. *: Statistically significant difference.

higher in Group M as compared to Group D patients (p=0.027, p=0.025, p=0.007, p=0.043, p=0.002, p=0.001) (Table III).

The changes in PaO_2 levels of all patients during the follow-up were statistically significantly higher from T2 than before treatment (T0)

(p=0.005, p=0.001, p<0.001, p<0.001, p=0.001, p<0.001, p<0.001, respectively) (Figure 2).

The change of PaO_2 level according to T0 was found to be statistically significant in each group (p<0.001) (Table IV). There was no statistically significant difference in the mean value of PaO_2 between the two groups.

When the groups were evaluated within themselves, the level of PaO_2 in Group D was always

Table III. pH, $PaCO_2$ values of discharged and exitus patients.

	Final status Discharge (Group D) Mean±SD	Exitus (Group M) Mean±SD	*p*-value
pH T0	7.44±0.01	7.44±0.07	0.545
pH T1	7.46±0.03	7.44±0.06	0.446
pH T2	7.45±0.03	7.42±0.10	0.400
pH T3	7.45±0.04	7.39±0.11	0.170
pH T4	7.45±0.04	7.38±0.09	0.052
pH T5	7.45±0.03	7.37±0.12	0.101
pH T6	7.44±0.03	7.36±0.12	0.204
pH T7	7.45±0.03	7.33±0.10	0.001
pH T_{final}	7.45±0.02	7.28±0.13	0.001
p	0.921	<0.001	
$PaCO_2$ T0, mmHg	36.1±6.5	39.8±15.8	0.789
$PaCO_2$ T1	36.9±6.2	42.2±13.7	0.615
$PaCO_2$ T2	37.6±4.9	46.2±14.1	0.076
$PaCO_2$ T3	38.0±6.1	46.2±11.0	0.027
$PaCO_2$ T4	40.3±3.1	46.6±8.7	0.025
$PaCO_2$ T5	41.9±3.1	49.1±7.9	0.007
$PaCO_2$ T6	42.6±2.3	48.7±7.6	0.043
$PaCO_2$ T7	41.6±2.6	53.5±12.5	0.002
$PaCO_{2final}$	41.8±2.5	57.3±14.1	0.001
p	0.004	0.001	

T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment. SD: Standard deviation.

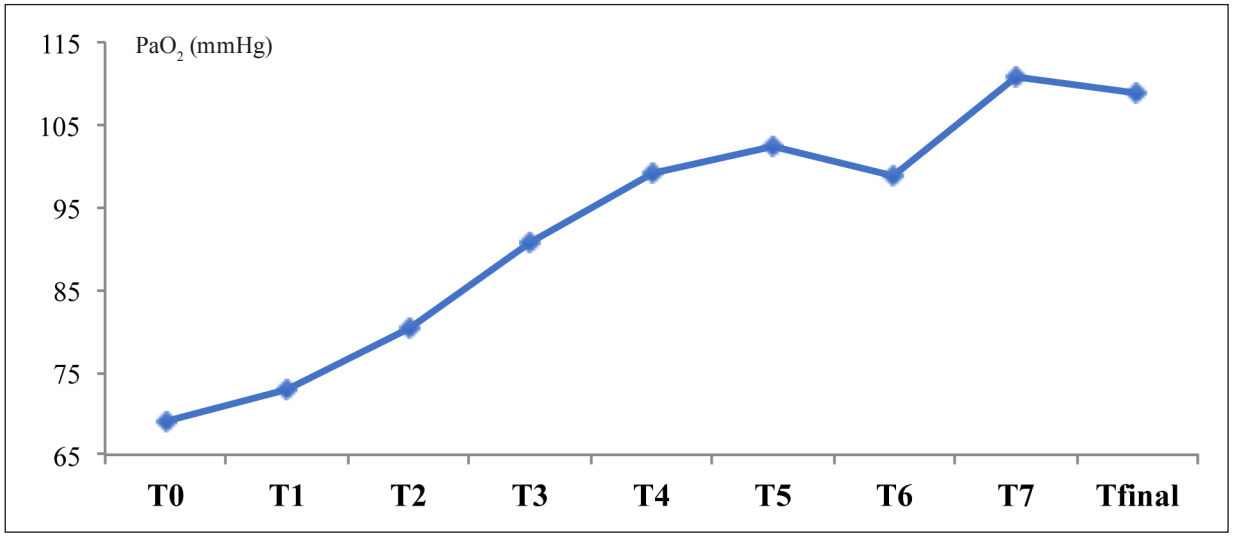

Figure 2. The Change in PaO_2 levels of patients after iloprost. PaO_2: partial oxygen pressure. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7. T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

significantly higher starting from T2 when compared with T0. On the other hand, the level of PaO_2 was significantly higher at T5-T_{final} as compared with T0 in Group M (Table IV).

When the groups were evaluated within themselves, while the change in $SatO_2$ levels compared to T0 in ICU follow-up was statistically significant in Group D (p<0.001), it was not significant in Group M (p=0.9066). In Group M patients, the mean value of $SatO_2$ from T5 was significantly lower than that of Group D patients (p=0.038, p=0.002, p=0.001, p=0.001) (Table IV).

Changes in $SatO_2$ levels were found to be statistically significant in all patients during the follow-up (p<0.001). $SatO_2$ was statistically significantly higher between T2 and T_{final} when compared with before treatment (T0) (p=0.005, p<0.001, p=0.001, p<0.001, p<0.001, p<0.001, p<0.001) (Table V).

The change in PaO_2/FiO_2 levels starting from T1 in both groups was statistically significantly higher than T0 (p=0.002, p<0.001). When the groups were evaluated within themselves according to T0, the change in PaO_2/FiO_2 levels was found to be statistically significant (p<0.001). The mean PaO_2/FiO_2 values of the patients in Group M from T5 were statistically significantly lower than the patients in Group D (p=0.023, p=0.005, p=0.011, p=0.002) (Table VI).

All patients had a statistically significant higher ROX Index from T4 than before treatment (T0) (p=0.001, p=0.006, p=0.008, p=0.001, p=0.005) (Table VII). In the discharged group, the ROX Index was statistically significantly higher starting from T1 when compared to T0.

While no significant difference was observed in SAP at follow-up, mean SAP values at T5-7 and T_{final} were significantly lower in Group M when compared to Group D (p=0.044, p=0.018, p=0.004) (Table VIII).

While no statistically significant change was observed in DAP levels in the follow-up; the mean DAP values at T7 and T_{final} were significantly lower in Group M when compared to Group D (p=0.021, p=0.005) (Table VIII).

Considering all patients, while no significant change was found in MAP during the follow-up, the mean MAP value at T7 and T_{final} in Group M were significantly lower than those in Group D (p=0.009, p=0.003) (Table VIII).

Table IV. PaO_2 (mmHg), $SatO_2$ (%) values of discharged and exitus patients.

	Final status		
	Discharge (Group D)	Exitus (Group M)	
	Mean±SD	Mean±SD	*p*-value
PaO_2 T0	64.6±15.5	72.2±21.6	0.482
PaO_2 T1	70.3±19.2	74.8±27.8	0.920
PaO_2 T2	78.4±14.3	81.9±32.1	0.763
PaO_2 T3	89.6±12.1	91.5±17.6	0.773
PaO_2 T4	100.6±25.2	98.4±22.3	0.833
PaO_2 T5	106.8±29.3	99.4±16.8	0.460
PaO_2 T6	110.4±28.2	90.6±30.6	0.139
PaO_2 T7	119.9±35.7	104.3±31.0	0.367
PaO_2T_{final}	122.3±41.5	99.5±29.5	0.192
p	<0.001	<0.001	
$SatO_2$ T0	87.3±3.9	87.8±3.6	0.754
$SatO_2$ T1	86.1±5.9	87.8±5.4	0.482
$SatO_2$ T2	90.6±3.8	89.6±3.4	0.551
$SatO_2$ T3	91.9±3.6	90.2±3.1	0.264
$SatO_2$ T4	93.2±3.2	90.6±3.2	0.075
$SatO_2$ T5	94.7±2.9	91.1±4.2	0.038
$SatO_2$ T6	95.3±3.0	90.6±3.2	0.002
$SatO_2$ T7	95.4±1.9	90.8±3.1	0.001
$SatO_2T_{final}$	96.2±1.3	90.6±3.1	0.001
p	<0.001	0.066	

PaO_2: Partial Oxygen pressure, $SatO_2$: Peripheral oxygen saturation, SD: Standard deviation. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment. SD: Standard deviation.

Table V. Changes in patients' $SatO_2$ (%) values compared to T0.

	Mean±SD	Min-Max (Median)	*p*-value
$SatO_2$ T0	87.8±3.6	83-97 (87)	
$SatO_2$ T1	87.8±5.4	80-97 (87)	0.543
$SatO_2$ T2	89.6±3.4	83-94 (91)	0.005
$SatO_2$ T3	90.2±3.1	85-94 (91)	<0.001
$SatO_2$ T4	90.6±3.2	85-96 (90)	0.001
$SatO_2$ T5	91.1±4.2	85-97 (90)	<0.001
$SatO_2$ T6	90.6±3.2	85-95 (91)	<0.001
$SatO_2$ T7	90.8±3.1	85-97 (91)	<0.001
$SatO_2$ T_{final}	90.6±3.1	87-97 (90)	<0.001

T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5:Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

Table VI. PO_2/FiO_2 values of the patients.

	Final status				
	Discharge (Group D)		Exitus (Group M)		
	Ort.±SD	Min-Max (median)	Ort.±SD	Min-Max (median)	*p*-value
PO_2/FiO_2 T0	129.1±25.8	95-170 (140)	130.5±20.3	103-160 (130)	0.886
PO_2/FiO_2 T1	139.9±28.7	100-190 (149)	140.1±20.1	105-170 (142)	0.986
PO_2/FiO_2 T2	148.0±35.6	105-220 (147)	155.0±20.5	105-190 (153)	0.564
PO_2/FiO_2 T3	165.2±30.8	120-230 (169)	154.4±43.8	16-190 (162)	0.947
PO_2/FiO_2 T4	175.6±15.9	150-200 (180)	169.8±15.8	149-200 (170)	0.415
PO_2/FiO_2 T5	199.7±23.1	164-230 (200)	178.2±17.9	150-220 (180)	0.023
PO_2/FiO_2 T6	216.3±24.8	180-250 (230)	180.8±26.4	140-230 (179)	0.005
PO_2/FiO_2 T7	233.3±32.3	200-300 (220)	192.5±34.6	145-250 (194)	0.011
PO_2/FiO_2 T_{final}	256.3±44.3	190-350 (240)	191.7±40.3	142-280 (190)	0.002
p	<0.001	<0.001			

PaO_2: Partial oxygen pressure, SD: Standard deviation, FiO_2: Fraction of inspired oxygen. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration.T5: Fifth day of iloprost administration.T6: Sixth day of iloprost administration.T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

Table VII. Changes in patients' ROX index values compared to T0.

	Mean±SD	*p*-value
ROX Index T0	6.7±1.4	
ROX Index T1	7.2±1.5	0.262
ROX Index T2	7.4±1.4	0.405
ROX Index T3	8.9±2.4	0.119
ROX Index T4	10.4±1.7	0.001
ROX Index T5	11.0±1.7	0.006
ROX Index T6	12.0±2.0	0.008
ROX Index T7	12.9±1.1	0.001
ROX Index T_{final}	13.7±1.9	0.005
p	<0.001	

ROX index: (SpO_2/FiO_2)/SS (respiratory rate). SpO2: Peripheral oxygen saturation. FiO_2: Fraction of Inspired Oxygen. SD: Standard deviation. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

Table VIII. SAP, DAP, MAP values of discharged and exitus patients.

	Final status		
	Discharge (Group D)	Exitus (Group M)	
	Mean±SD	Mean±SD	*p*-value
SAP T0, mmHg	121.1±15.3	124.2±16.5	0.658
SAPT1	117.1±12.6	122.6±14.6	0.370
SAP T2	120.4±10.9	124.8±12.8	0.417
SAP T3	130.8±20.8	125.1±14.9	0.462
SAP T4	125.9±16.8	122.5±16.1	0.525
SAP T5	130.8±15.9	119.3±9.1	0.044
SAP T6	125.1±11.1	122.5±14.0	0.651
SAP T7	125.8±12.2	110.2±14.9	0.018
SAP T_{final}	130.0±12.3	103.7±23.5	0.004
***p*#**	0.202	0.004	
DAP T0, mmHg	63.7±11.7	64.2±10.9	0.921
DAP T1	57.7±7.5	63.6±10.0	0.146
DAP T2	62.0±5.3	60.7±6.4	0.618
DAP T3	66.9±10.8	62.2±9.1	0.278
DAP T4	64.3±11.4	63.0±9.2	0.765
DAP T5	64.6±7.0	61.1±9.5	0.361
DAP T6	63.0±6.6	62.4±8.2	0.854
DAP T7	67.0±9.2	55.8±11.0	0.021
DA T_{final}	67.0±9.2	52.2±11.8	0.005
***p*#**	0.202	0.004	
MAP T0, mmHg	81.8±10.6	84.2±11.5	0.628
MAP T1	78.9±9.6	83.2±9.9	0.329
MAP T2	81.7±6.3	82.1±6.2	0.881
MAP T3	88.2±13.3	83.1±10.2	0.315
MAP T4	84.8±12.6	82.8±9.2	0.681
MAP T5	86.7±9.2	80.4±8.3	0.110
MAP T6	83.6±5.1	82.4±9.2	0.734
MAP T7	86.8±8.3	74.0±11.4	0.009
MAP T_{final}	87.9±7.8	69.3±15.4	0.003
***p*#**	0.279	0.002	

#Repeated measurement analysis of variance. SAP: systolic arterial pressure, DAB: Diastolic arterial pressure, MAP: Mean arterial pressure, SD: Standard deviation. T0: before starting iloprost. At the end of the iloprost infusion for T1-T7 – T1: First day of iloprost administration. T2: Second day of iloprost administration. T3: Third day of iloprost administration. T4: Fourth day of iloprost administration. T5: Fifth day of iloprost administration. T6: Sixth day of iloprost administration. T7: Seventh day of iloprost administration. T_{final}: The day after the end of treatment.

Considering all patients, no significant change was found in HR levels during follow-up. When the groups were compared, no statistically significant difference was found in the mean HR values.

Discussion

The use of iloprost is known in conditions such as sepsis, ARDS, pulmonary arterial hypertension, peripheral artery disease, and ischemia-reperfusion injury[4,11-15]. Prospective studies[16,17] on its use in COVID-19 patients with severe pneumonia are ongoing. We believe that our study can contribute to the existing literature.

Lactate level is an important indicator of tissue perfusion and mortality in sepsis. It has been shown[18] that rather than a single measurement, the demonstration of lactate clearance by repeated measurements is important in evaluating the efficacy of fluid resuscitation, especially in patients with a lactate level above 2 mmol/L. When all patients were evaluated in our study, the tendency of lactate to decrease after iloprost treatment suggests the positive effects of iloprost on vascular bed and perfusion.

Bruno et al[19] found that baseline lactate ≥2 mmol/L was associated with higher ICU stay and 3-month mortality (71%, 57%) in COVID-19 patients aged 70 years and older. In our study, a significant correlation was observed between older age, high lactate values at admission, high APACHE II and SOFA scores,

and mortality. Iloprost, lactate levels remained high in Group M.

The decrease in $PaCO_2$ when PaO_2 is low in COVID-19 patients is explained by the deterioration of the passage of oxygen through the alveolocapillary membrane due to the right-to-left shunt that develops as a result of impaired capillary perfusion, increased hemoglobin oxygen affinity, and consequently increased alveolar ventilation[20]. When the baseline values of our patients were compared, hypercarbia, seen in all patients from T2 and in Group M starting from T3 when compared to Group D, can be explained by the decreased shunt in the patient group who were discharged after the HFNO in ICU follow-up, mechanical ventilation, and medical treatment. At the same time, this hypercarbia and gradual increase in lactate seems to have caused a decrease in pH values at T7 and T_{final} in Group M.

The significant increase in PaO_2 levels from the 2nd day in patients treated with iloprost shows its positive effects on COVID-19. However, this positive improvement of PaO_2 did not influence mortality. The positive change in PaO_2 seen in both groups was not seen for $SatO_2$ in Group M.

While the mean PaO_2/FiO_2 was 130.5 during admission to the Intensive Care Unit in all patients included in the study, after starting iloprost, the PaO_2/FiO_2 value increased significantly from T1 and remained high (191.7) after the end of treatment (T_{final}). Although the change within the groups is significant, the fact that the PaO_2/FiO_2 values of the patients in Group M were lower at T5 and later compared to Group D may suggest that the relationship between iloprost administration and the PaO_2/FiO_2 trend will be a guide for the time of discharge. Moezinia et al[21], stated that oxygen requirements of all patients decreased and PaO_2/FiO_2 increased from 155 to 329 in their case series in which data of 3 patients, to whom 0.5 mg/kg/min i.v. iloprost was administered for 5 days and was evaluated. Considering that these patients were followed-up in the service, this may explain the higher PaO_2/FiO_2 values compared to our patient group.

It is seen that the ROX index value, which was 6.7 at the time of admission to the Intensive Care Unit, started to increase after the start of iloprost and the increase was statistically significant from T4 (4th day of iloprost administration). This increase in patients receiving HFNO is consistent with previously studied[22,23] "weaning cut-off values". Suliman et al[24], found in their study with 69 COVID-19 patients receiving HFNO that a ROX index value ≤25.26 on the first day is a predictive factor for intubation (with 90.2% sensitivity and 75% specificity). The researchers[24] attributed such a high cut-off value to the heterogeneous nature of the patient group. In a study investigating the role of the ROX index in the initial assessment of COVID-19 patients in the Emergency Department were examined until discharge or death, and a ROX index <22.3 was found[25] to be associated with higher 30-day mortality. Of the patients who were discharged, the patients in the exitus group were intubated on the 3rd day of the ICU and continued to receive iloprost. Considering the ROX index values at T1 and T2 before intubation, mean ROX index values in Group M (T1; 6.9±1.9 T2; 6.9±1.6) were found to be significantly lower compared to Group D (T1; 7.5±0.8 T2; 7.7±1.4) (p=0.417 and p=0.420). While there was a significant increase in the ROX index at all times according to T0 (before starting iloprost treatment) in the discharged group, there was no significant change in the exitus group, and this finding also confirms the importance of the ROX index in prognostic follow-up in this group of patients receiving iloprost.

There is evidence[7,8] that iloprost has no adverse effects on hemodynamics. It was observed[26] that iloprost did not impair hemodynamics in patients to whom IV iloprost was administered at a dose of 0.5 ng/kg/min for 24 hours and 1 ng/kg/min[27] for 6 hours. The lack of a significant effect of iloprost application on SAP, DAP, MAP, and HR in the ICU follow-up period, and lower DAP and MAP values at T7, T_{final}, and lower SAP values at T5-T7 and T_{final} in our patients who were in the exitus group compared to those in the discharged group, may demonstrate that administration of iloprost is hemodynamically safe. Although relatively higher infusion doses and durations were applied in our patients, a significant hemodynamic instability was not observed (although it was more prominent, especially in the discharged group). This may shed light on prospective studies in which higher doses of iloprost are administered intravenously to a larger patient group.

Conclusions

In conclusion, although iloprost did not have a positive effect on mortality or mechanical ventilation requirement with the data we obtained from our limited number of patients, its IV administration can improve clinical parameters by improving oxygenation without disturbing he-

modynamics in COVID-19 patients with severe ARDS. However, we think that our study will shed light on prospective randomized controlled studies with larger patient numbers.

Ethics Approval
The ethics approval was obtained from the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital. The date/No. of approval: 09.02.2021/ E-48670771-514.10.

Conflict of Interest
All authors declare that they do not have any conflict of interest regarding the study.

Informed Consent
Informed consent was obtained from the relatives or from the patients included in the study.

ORCID ID
Rabia Sarı: 0000-0002-7597-8297
Kamuran Uluç: 0000-0001-6128-0462
Şükran Merve Çolakoğlu: 0000-0003-3739-4595
Cansu Kılınç Berktaş: 0000-0002-5387-0734
Sinan Mutlu: 0000-0003-3801-0936
Namigar Turgut: 0000-0003-0252-3377

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Availability of Data and Materials
The data generated and analyzed during the study are available from the corresponding author. They are not available publicly.

Authors' Contributions
The concept for research or article/hypothesis generation: Rabia Sarı Küçük, Kamuran Uluç. Planning the methods to generate the hypothesis: Rabia Sarı Küçük, Namigar Turgut, Şükran Merve Çolakoğlu. Supervision and responsibility for the organization and course of the project and manuscript preparation: Rabia Sarı Küçük, Namigar Turgut, Kamuran Uluç, Şükran Merve Çolakoğlu. Supplying equipment, space, and personnel vital to the Project: Rabia Sarı Küçük, Kamuran Uluç, Namigar Turgut, Sinan Mutlu, Cansu Kılınç Berktaş. Discussion of the results, and approval of the final version of the work: Rabia Sarı Küçük, Kamuran Uluç, Namigar Turgut.

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