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Coronavirus Pandemic

Survival of critically ill patients with COVID-19 pneumonia-a single-center experience

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Abstract

Introduction: The aim of the study was to determine the survival probability of critically ill patients with COVID-19 infection who needed mechanical ventilation and to determine the efficacy of Tocilizumab use.

Methodology: The study was designed as a retrospective analysis of consecutive patients older than 18 years, treated in an intensive care unit. The criteria for admission to the intensive care unit was severe respiratory failure requiring mechanical ventilation. All patients received corticosteroid therapy (methylprednisolone 1-2 mg/kg). Tocilizumab was used at a dose of 8 mg/kg in patients with a severe form of the disease (onset, or developed ARDS), followed by cytokine storm (IL-6 ≥ 40 ng/L and CRP ≥ 50 mg/L).

Results: 88 patients were included in the study. Intrahospital mortality was 48.86%. No statistically significant difference was observed between patients with and without tocilizumab therapy. In the group of patients in whom this therapy was applied, the values of intrahospital survival were 45.7%, while in the group without this therapy the probability of intrahospital survival was only 0.93%. The probability of survival in the group with noninvasive mechanical ventilation (NIV) was 94.7%, while in the group with invasive mechanical ventilation (IMV) 0.78%. The duration of symptoms before hospitalization (RR-1.088 CI 1.025-1.155, $p < 0.05$), as well as the duration of IMV (RR-0.906 CI 0.841-0.976, $p < 0.05$), were shown to be an independent predictor of poor outcome.

Conclusions: The mortality of patients with the most severe form of respiratory failure caused by COVID-19 infection remains high. Independent predictors of poor outcomes were needed for invasive mechanical ventilation and the duration of symptoms before hospitalization or late initiation of appropriate therapy.

Key words: Pneumonia; Tocilizumab; mechanical ventilation; survival; predictors.

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Introduction

According to the World Health Organization, the number of people infected with Coronavirus disease 2019 (COVID-19) worldwide exceeds 567 million, with more than 6 million deaths [1]. Studies have shown that between 5-14% of infected people develop moderate to severe forms of illness [2,3]. Respiratory failure followed by multiorgan dysfunction and shock were the most common cause of death. The host immune response is thought to be crucial in the pathophysiology of infection. The use of glucocorticoids has been shown to be the only therapy that improves survival in critically ill patients with COVID-19 [4].

Previous studies have confirmed a link between IL-6, CRP, other inflammatory proteins, and disease severity [5,6]. Tocilizumab, a monoclonal antibody that binds to IL-6 receptor, have shown some benefit in the treatment of some inflammatory disease [7]. Results of randomized studies in COVID-19 treatment are different. There is proof that the use of Tocilizumab reduces the risk of mechanical ventilation, but without a significant effect on mortality [8-13]. Also, there is proof that early use of Tocilizumab slows virus replication and the incidence of complications [14].

The study aimed to determine the survival probability of critically ill patients with COVID-19 infection who needed mechanical ventilation and to determine the efficacy of Tocilizumab use.

Methodology

Study design and participants

The study was designed as a retrospective analysis of consecutive patients older than 18 years, treated in

the intensive care unit at the pulmonology clinic of the Clinical Center of Serbia between 20th November 2020 and 20th November 2021. Written consent of patients was not required, due to the study design.

Since the number of infected patients was high, numerous hospitals were converted into Covid hospitals, where patients with moderate Covid pneumonia were treated. In case of clinical or radiographic deterioration, they were transferred into one of the intensive care units. Thus, the study included patients who were transferred from other Covid hospitals, but also patients from the pulmonology clinic who required intensive care.

Criteria for admission to the intensive care unit were severe respiratory failure requiring mechanical ventilation (invasive and/or non-invasive), followed by worsening of respiratory function and radiograph progression with previously laboratory-confirmed COVID-19 infection. Patients on high-flow with the flow rate of 70 L/min and 100% FiO_2 who had PaO_2 less than 8 kPa and SpO_2 less than 90% were transferred to the intensive care unit.

Therapy

Treatment of all patients was based on a national protocol for severe forms of COVID-19 infections. All patients received corticosteroid therapy (methylprednisolone 1-2 mg per kg actual body weight), followed by a standard multivitamin, anticoagulant, gastroprotective, and antibiotic therapy based on laboratory and microbiological parameters.

Tocilizumab was used in a dose of 8 mg/kg actual body weight up to 800 mg in infusion for 60 minutes in patients with a severe form of the disease (onset, or developed ARDS), followed by a cytokine storm.

Administration of Tocilizumab was repeated in the same dose after 12-24 hours if there was no clinical benefit. Criteria for Tocilizumab administration were: IL-6 ≥ 40 ng/L followed by an increase CRP > 50 (or triple increase in CRP concentration during 48 hours if the level of IL6 cannot be measured), radiographic signs of massive Covid pneumonia followed by respiratory failure. The decision on the use of Tocilizumab was made in consultation (Concilium consisting of a pulmonologist, infectiologist, and anesthesiologist).

Mechanical ventilation in most cases begins with non-invasive mechanical ventilation with CPAP mask, full face mask, and helmet followed by changing body position and proning. In cases when those methods were not successful patients were intubated.

Outcomes

The primary objective of the study was to determine overall in-hospital mortality and survival, while the secondary objective was to determine the effect of Tocilizumab administration on the observed outcomes.

Statistical analysis

SPSS software version 28 (SPSS Inc, Chicago, IL, USA) was used for statistical data processing. The choice of tests for the analysis of numerical features of

Table 1. Characteristics of patients.

Variable	Survival (N = 45)	Non survival (N = 43)	*p*
Age	62.18 ± 12.82	66.56 ± 12.56	0.216
Gender (Male/Female)	21 (46.7%) / 24 (53.3%)	27 (62.8%) / 16 (37.2%)	0.141
Symptoms duration before hospitalization in days	9.93 ± 6.92	11.37 ± 7.61	0.736
Previous treatment: No / Primary care/Hospital	11 (24.4%) / 8 (17.8%) / 26 (57.8%)	4 (9.3%) / 7 (16.3%) / 32 (74.4%)	0.142
Antibiotic treatment No / Yes	10 (22.2%) / 35 (77.8%)	2 (4.7%) / 41 (95.3%)	0.016
Comorbidity No / Yes	8 (17.8%) / 37 (82.2%)	5 (38.5%) / 38 (50.7%)	0.416
Hypertension	20 (44.4%)	15 (34.9%)	0.360
Cardiomyopathy	1 (2.2%)	6 (14%)	0.042
Atrial fibrillation	0 (0%)	1 (2.3%)	0.304
COPD	7 (15.6%)	5 (11.6%)	0.591
DM Oral therapy / insulin	11 (24.4%) / 1 (2.2%)	13 (30.2%) / 4 (9.3%)	0.252
Smoker	5 (11.6%)	0 (0%)	0.021
Tocilizumab	22 (48.9%)	11 (25.6%)	0.029
Duration of symptoms before Tozilizumab in days	9.59 ± 7.54	12.82 ± 10.89	0.645
IMV	17 (37.8%)	42 (97.7%)	0.000
Duration of NIMV	6.84 ± 5.03	5.17 ± 4.66	0.100
Duration of IMV	7.17 ± 5.03	5.67 ± 4.68	0.247
Total duration of MV	8.49 ± 5.97	9.74 ± 6.91	0.479
Treatment duration	9.60 ± 7.83	9.09 ± 5.96	0.701

*COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; IMV: Invasive mechanical ventilation; NIMV: noninvasive mechanical ventilation; MV: mechanical ventilation.

observations depended on the nature of their distribution, which was examined using the Koglomorov – Smirnov test. To test the difference between the subjects from the group of survivors and the group of deaths, the Mann-Whitney U test was used while Student's t-test was used for non-parametric data. To compare the attributive characteristics of the observations between the analyzed groups of subjects, Pearson's χ^2 test was used. Survival predictors were examined by Cox regression analysis. The limit value for accepting the hypothesis of the existence of a difference between the tested groups in the analyzed variables was set at $p < 0.05$.

Results

Ninety patients were included in the study between 20th November 2020 and January 2021, all of whom were in ICU at the pulmonology clinic, at the University Clinical Centre of Serbia. Two patients were excluded from the study due to the need for surgical treatment which couldn't be done in this center. The final number of patients included in the study was 88. Among the 88 patients included in the study, 43 died in ICU. Intrahospital mortality was 48.86% (43/88).

Patient basic characteristics are shown in Table 1. The average age of surviving and non-surviving patients was approximately the same, no statistical significance was registered. Although more men were in the non-survival group (62.8% vs. 46.7%) the differences were not statistically significant. Patients from the non-survival group were reported later to the hospital, the duration of symptoms onset before hospitalization was longer in this group. Also, a higher percentage of patients from the non-survived group were hospital treated before admission to the ICU (74.4% vs. 57.8%, $p > 0.05$). More patients from the non-survived group were treated with antibiotics before ICU admission (95.3% vs. 77.8%, $p < 0.05$).

There were no differences in frequency of comorbidity between these two groups. The most often registered comorbidity was arterial hypertension- 20 (44.4%) survived patients and 15 (34.9%) from the non-survived group. In patients who had a lethal outcome, cardiomyopathy was present in a significantly higher percentage, as it was registered in 14% of non-survived compared to 2.2% of the survived group, which was statistically significant ($p = 0.042$). There was also statistical significance in terms of smoking habits, it was more often registered in the survived group (11.6% vs. 0%, $p < 0.05$)

A significantly higher percentage of patients from the non-survived group required invasive mechanical ventilation compared to patients from survived group (97.7% vs. 37.8%), where statistical significance was registered ($p < 0.05$) (Figure 1). There was no significant difference in the duration of non-invasive, invasive, and total duration of mechanical ventilation between the examined groups of patients. Also, the total length of treatment for patients was approximately the same, no significant difference was registered.

37.5% of the patients were treated with Tocilizumab, 48.9% of patients from the survival group, and 25.6% of patients from the non-survival group, where a statistically significant difference ($p < 0.05$) was registered in terms of the primary outcome, survival (Figure 2). The duration of disease symptoms until the use of Tocilizumab was longer in the non-survival group compared to the group of survivors, but without a statistically significant difference (12.82 ± 10.89 vs. 9.59 ± 7.54, $p < 0.05$).

Table 2 shows the values of intrahospital survival, in groups with and without observed risk factors and applied therapeutic procedures.

Figure 1. Impact of mechanical ventilation on survival.

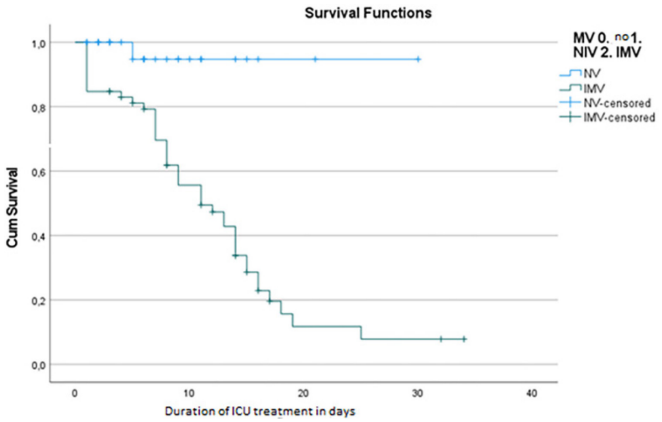

Figure 2. Impact of Tocilizumab use on survival.

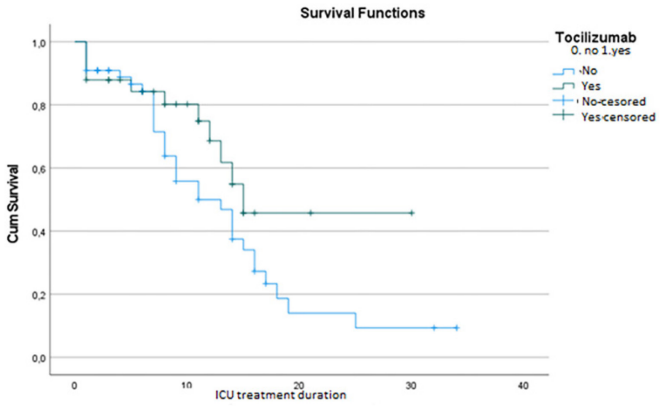

Table 2. Intrahospital survival.

Observed factors		Intrahospital survival (% (Med (95%CI)))	Significance (*p* -value)
Overall survival		15.7% / 14 (11.98 - 16.00)	-
Gender	Male	13.6% / 14 (10.59 - 17.41)	0.200
	Female	30.1% / 14 (9.20 - 18.80)	
Antibiotic treatment	No	0% / 11 (/)	0.046
	Yes	14.7% / 13 (9.76 - 16.24)	
Comorbidity	No	35.0% / 18 (9.72 - 26.28)	0.156
	Yes	11.7% / 14 (11.84 - 16.16)	
Hypertension	No	14.3% / 13 (9.77 - 16.23)	0.451
	Yes	16.0% / 15 (13.40 - 16.60)	
Cardiomyopathy	No	17.4% / 14 (12.20 - 15.8)	0.019
	Yes	0% / 8 (5.43 - 10.57)	
Angina pectoris	No	16.2% / 14 (11.85 - 16.15)	0.214
	Yes	33.3% / 11 (0 - 25.97)	
COPD	No	15.9% / 14 (12.13 - 15.87)	0.307
	Yes	26.8% / 25 (8.28 - 41.72)	
Diabetes mellitus	No	15.9% / 14 (12.08 - 15.91)	0.122
	Oral therapy	26.8% / 12 (7.56 - 16.44)	
	Insulin	0% / 7 (2.02 - 11.98)	
Tocilizumab	No	0.93% / 11 (6.74 - 15.27)	0.091
	Yes	45.7% / 15 (8.02 - 17.98)	
NIMV/IMV	NIMV	94.7%	0.001
	IMV	0.78% / 11 (6.76 - 15.24)	

*CI: confidence interval; COPD: chronic obstructive pulmonary disease; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation.

Table 3. Univariate COX regression analysis.

Variable	HR	95% CI	*p* value
Age	1.016	0.988 - 1.045	0.268
Gender	0.676	0.363 - 1.260	0.217
Symptoms duration before hospitalization	1.050	1.004 - 1.098	0.033
Antibiotic therapy before ICU admission	3.684	0.888 - 18.285	0.072
Comorbidities	1.915	0.748 - 4.901	0.176
Hypertension	0.790	0.420 - 1.489	0.466
Cardiomyopathy	2.698	1.103 - 6.604	0.030
Atrial fibrillation	1.298	0.177 - 9.544	0.798
Angina pectoris	2.053	0.619 - 6.809	0.239
Chronic obstructive pulmonary disease	0.620	0.239 - 1.609	0.326
Diabetes mellitus	1.543	0.966 - 2.466	0.070
Smoker	0.045	0.000 - 16.427	0.303
Tocilizumab treatment	0.567	0.285 - 1.130	0.107
Duration of disease to Tocilizumab in days	1.032	0.976 - 1.092	0.266
Mechanical ventilation	15.305	2.104 - 11.345	0.007
Number of days of using NIMV	0.908	0.846 - 0.974	0.007
Number of days using IMV	0.891	0.826 - 0.951	0.001
Total duration of MV in days	0.891	0.837 - 0.948	0.000

**HR: hazard ratio; CI: confidence interval; ICU: intensive care unit; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; MV: mechanical ventilation

Table 4. Multivariant Cox regression analysis.

Variable	HR	95% CI	*p* value
Symptoms duration before hospitalization	1.088	1.025 - 1.155	0.005
Cardiomyopathy	1.810	0.629 - 5.210	0.271
Mechanical ventilation	49385.743	0.000 - /	0.984
Number of days on non-invasive MV	0.980	0.906 - 1.059	0.606
Number of days on invasive MV	0.906	0.841 - 0.976	0.009

*HR: hazard ratio; CI: confidence interval; MV: mechanical ventilation.

Patients with cardiomyopathy had a statistically significantly worse survival rate than patients without cardiomyopathy. No statistically significant difference was observed between patients with and without tocilizumab therapy, but higher survival was observed in the group with this therapy. In the group of patients in whom this therapy was applied, the values of intrahospital survival were 45.7%, while in the group without this therapy the probability of intrahospital survival was only 0.93%. A statistically significant difference was observed between respondents with NIV and IMV. The probability of survival in the group with NIV was 94.7%, while in the group with IMV 0.78%.

Table 3 shows the results of Cox's regression analysis. Age and sex did not affect survival. The duration of symptoms before hospitalization was determined as a predictor of poorer survival with HR 1.050 (CI 1.004-1.098, $p < 0.05$). The use of antibiotic therapy, before admission to the ICU, affected better survival with an HR of 3.68 (CI 0.888-18.285, $p > 0.005$), no statistically significant difference was registered, only a trend. Patients with cardiomyopathy had a 2.69-fold higher risk of dying compared with patients without cardiomyopathy (CI 1.103-6.604, $p < 0.05$), as well as diabetes mellitus where the relative risk of dying was 1,543 times higher in the group of patients who had diabetes compared with patients who did not have diabetes (CI 0.966-2.466, $p > 0.05$). Tocilizumab did not stand out as a predictor of better survival of our patients, nor did the duration of the disease until the use of tocilizumab therapy. The strongest predictor was invasive mechanical ventilation, patients who required invasive mechanical ventilation had a 15,305 higher risk of dying compared to patients who were not invasively mechanically ventilated (CI 2.104-11.345, $p < 0.05$). It has also been shown that the duration of mechanical ventilation, both non-invasive and invasive, but also the total duration of mechanical ventilation affected death. Patients who required mechanical ventilation for a longer period of time had a higher risk of dying, where a statistically significant difference was registered.

The results of the multivariate regression analysis are shown in Table 4. The duration of symptoms before hospitalization (RR-1.088 CI 1.025-1.155, $p < 0.05$), as well as the duration of invasive mechanical ventilation (RR-0.906 CI 0.841-0.976, $p < 0.05$), were shown to be an independent predictor of poor outcome.

Discussion

The results of our study show that the mortality of critically ill patients with COVID-19 infection who required mechanical ventilation is high (45%), which corresponds to previously published data [15-17]. We have also shown that in addition to invasive mechanical lung ventilation, the duration of symptoms before hospitalization is an independent predictor of mortality in these patients. With the onset of the pandemic, death rates were high. In patients admitted to the ICU, they ranged up to 62%, while in mechanically ventilated patients they were up to 97% [18,19]. It was also shown that the mortality of intubated patients from COVID-19 infection was far higher compared to the mortality of patients with other viral pneumonia, which also required mechanical lung ventilation (67% vs 22%) [20]. Such high mortality rates have led to concerns about whether mechanical ventilation should be avoided in COVID-19 patients [21]. On the other hand, the results of Auld *et al.* showed that the mortality rate was significantly lower and amounted to 35.7% in a sample of 217 patients [22]. They showed that the factors that influenced higher mortality were older age, lower BMI, chronic renal insufficiencies, higher SOFA score on admission, lower PO_2/FiO_2 ratio, higher D-dimer values, higher CRP, use of invasive mechanical ventilation, vasopressor and renal replacement therapy, inhaled vasopressors. Ramosaço *et al*. showed that the presence of comorbidities such as arterial hypertension and diabetes mellitus were not significant risk factors for mortality [23].

The recently published results of the same group of authors showed a significant decline in the mortality rate. In a sample of 1,686 critically ill patients, the mortality rate was 29.7% [24]. In their meta-analysis, Amstrong *et al*. showed a significant decline in mortality rates of approximately 10% between March and May 2020 [25].

Better patient survival is certainly due to the progress in understanding the pathophysiology of the disease and the implementation of appropriate protocols. Systemic inflammation is crucial in disease progression and respiratory failure. Thus, the RECOVERY study demonstrated better survival in patients treated with methylprednisolone [4]. Numerous studies have examined the effects of other immunomodulatory drugs on treatment outcomes. Most studies have been done on the use of Tocilizumab, an IL-6 receptor inhibitor, and the data are quite inconsistent. Primarily because the studies differ in design, patient selection, the severity of respiratory failure at the time of drug administration, recommended dose, time of administration, and follow-up outcomes. In our study, 37.5% of patients received Tocilizumab, 48.9% from the survival group versus 25.6% from the

non-survived group, which was statistically significant (p = 0.029). Also, the time from the onset of disease symptoms to the use of Tocilizumab was shorter in the group of survivors, but without a statistically significant difference. These results are consistent with previously published studies.

In a study based on 3,924 critically ill patients, Gupta *et al.* showed that patients treated with Tocilizumab within 2 days of admission to the ICU had a lower risk of death compared with patients who did not receive Tocilizumab (HR, 0.71; 95% CI, 0.56 - 0.92). In contrast to our study, patients who were treated with Tocilizumab (433 patients, 11%) were significantly younger and had fewer comorbidities. A significantly lower percentage of patients were treated with concomitant corticosteroids: 18.7% of the group treated with Tocilizumab and 12.6% of the control group, in contrast to our study where all patients were treated with corticosteroids. Mortality was 39.3% (8.2% of patients were still hospitalized at the end of follow-up), 28.9% in the Tocilizumab-treated group versus 40.6% in the control group [26]. Like other studies [27,28] Gupta *et al*. have shown that early administration of Tocilizumab, within 3 days of disease onset, has the best effect on treatment outcome [26]. The REMAp-CAP study also showed better survival in patients treated with Tocilizumab. In this study, more than 80% of patients were treated with corticosteroids and included patients who required respiratory or cardiovascular support after admission to the ICU. Invasive mechanical ventilation was applied in 29%, non-invasive in 42%, and HF nasal cannula in 29% of patients. Mortality in the IL-6 receptor antagonist group was 27%, while in the control group it was 36%, and odds ratios for in-hospital survival were 1.64 (95% CI, 1.14 to 2.35) for Tocilizumab and 2.01 (95% CI, 1.18 to 4.71) for Sarilumab as compared with control. They showed that a group of patients treated with an IL-6 receptor antagonist had better 90-day survival, thus to ICU and hospital discharge. Also in this study, emphasis was placed on early initiation of therapy, within 24 hours of admission to the ICU, assuming that the maximum effect of therapy can be expected in critically ill patients before irreversible changes occur [29].

Somers *et al.* also showed positive effects of Tocilizumab in mechanically ventilated patients. The drug was administered within 48 hours of intubation. In addition to the positive effect on survival, they showed that its use affected the frequency of superinfections, pneumonia, and bloodstream infections in 39% of patients (54% vs. 26%; $p < 0.001$), but they did not affect the overall survival of patients [30]. A RECOVERY study in a sample of 4,116 patients showed that patients treated with Tocilizumab had better survival (31% vs 35%, $p = 0.0028$), as well as less likely to require invasive mechanical ventilation or have a fatal outcome [4].

On the other hand, the results of several smaller studies, which included a total of 933 patients, failed to prove the benefits of Tocilizumab treatment. Patients included in these studies generally had a lower degree of respiratory failure. In The BACC-Bay trial [8] and RCT-TCZ-COVID-19 [10] patients were treated with either an oxygen mask with a flow of no more than 10 L or an HF nasal cannula, while in TOCIBRAS [13] and COVACTA [12] patients on various modes of respiratory support, from O_2 therapy up to invasive mechanical ventilation. In contrast to the above studies, the patients included in our study had the most severe degree of respiratory failure, who did not respond to O_2 therapy (HF or simply O_2 mask), but all required mechanical ventilation, which is very different from the previously mentioned studies. The criteria for the use of Tocilizumab were: elevated CRP and IL values, which is generally consistent with most studies. In the RECOVERY study, the inclusion criteria was CRP greater than 75 mg/L [4], in TOCIBRAS and BAC-Bay greater than 50 mg/L [13,8]. The REMAP CAP study showed that the best effect of Tocilizumab was achieved in a group of patients with CRP over 150 mg/L [28]. It was concluded that patients with elevated CRP values (above 75-150 mg/L) are likely to benefit from Tocilizumab, but there are still no clear recommendations for its use in patients with poor oxygenation and low inflammatory parameters [31].

Conclusions

The results of our study indicate that the mortality of patients with the most severe form of respiratory failure caused by Covid-19 infection remains high. An independent predictor of poor outcome were need for invasive mechanical ventilation and the duration of symptoms before hospitalization or late initiation of appropriate therapy. Patients treated with Tocilizumab had a lower mortality rate, but in such a small sample, it did not stand out as an independent predictor. Future studies are necessary to obtain an answer as to what is the optimal dose, the time of drug administration concerning the onset of the disease and the duration of symptoms, and the degree of respiratory failure.

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