Cyclosporine A therapy in patients with COVID-19 and failure of immunosuppression therapy: a retrospective cohort propensity-score matched analysis

Применение циклоспорина А у пациентов с COVID-19 при неэффективности первичной иммуносупрессии: ретроспективное когортное псевдорандомизированное исследование

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Abstract

INTRODUCTION: Therapy of COVID-19 patients with progressive lung damage after the use of glucocorticosteroids (GCS) and interleukin-6 inhibitors (IIL-6) has not yet been developed. **OBJECTIVE:** Assessment of the effectiveness of cyclosporine A in patients with COVID-19 with progression of lung damage and hypoxemic acute respiratory failure, who received therapy with GCS and IIL-6. **MATERIALS AND METHODS:** A retrospective cohort propensity-score matched analysis ($n = 98$). Cyclosporine A was prescribed in the first 72–96 hours after IIL-6 administration when the patient's condition worsened. The patients of comparison group corresponded to the study group, but did not receive cyclosporine A therapy. The primary end point was in-hospital mortality. Secondary endpoints — duration of hospitalization, number of patients admitted to the intensive care unit (ICU), need for respiratory support. **RESULTS:** Mortality was 12 (22) % in the cyclosporine group and 27 (61) % in the comparison group, $p = 0.001$ (hazard ratio [HR] 2.00 (1.12–3.48), $p = 0.018$), ICU admission rate 14 (26) % *vs* 29 (66) %, $p = 0.001$, respectively. In the cyclosporine group on day 7 CT-4, there were 26 % of patients *vs*

Реферат

АКТУАЛЬНОСТЬ: Терапия пациентов с новой коронавирусной инфекцией (COronaVIrus Disease 2019 — COVID-19) при прогрессирующем поражении легких на фоне применения глюкокортикостероидов (ГКС) и ингибиторов интерлейкина-6 (ИИЛ-6) до сих пор не разработана. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** оценка эффективности циклоспорина А у пациентов с COVID-19 при прогрессировании поражения легких и гипоксемической острой дыхательной недостаточностью, получивших патогенетическую терапию ГКС и ИИЛ-6. **МАТЕРИАЛЫ И МЕТОДЫ:** Ретроспективное когортное псевдорандомизированное моноцентровое исследование ($n = 98$). Циклоспорин А назначали в первые 72–96 ч после введения ИИЛ-6 при ухудшении состояния пациентов. Пациенты группы сравнения соответствовали основной группе, но не получали терапию циклоспорином А. Первичная конечная точка — госпитальная летальность. Вторичные конечные точки — длительность госпитализации, количество пациентов, поступивших в отделение реанимации и интенсивной терапии (ОРИТ), потребность в респираторной поддержке. **РЕЗУЛЬТАТЫ:**

52 % in the control group, $p = 0.014$, the need for respiratory support (37 % *vs* 63.6 %, $p = 0.011$); saturation 88 % (82–93) *vs* 80 % (70–86), $p = 0.001$, respectively. The need for respiratory support at day 11 after IIL-6 increased the likelihood of death (HR 7.10 (2.5–20), $p = 0.001$). Risk factors for death: age over 57.5 years, body mass index over 30 kg/m^2, hemoglobin oxygen saturation below 85.5 % on the day of IIL-6 application. Duration of hospitalization was 18.5 (14–24) days *vs* 18 (12–24) days, $p = 0.778$. **CONCLUSIONS:** Cyclosporine A in addition to GCS and IIL-6 for COVID-19 therapy may reduce mortality, ICU admissions, and respiratory support requirements.

KEYWORDS: cyclosporine A, COVID-19, SARS-CoV-2, mortality, respiratory support

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Летальность составила 12 (22) % в группе циклоспорина и 27 (61) % в группе сравнения, $p = 0{,}001$ (относительный риск (ОР) 2,00 [1,12–3,48], $p = 0{,}018$), частота поступления в ОРИТ 14 (26 %) против 29 (66 %), $p = 0{,}001$ соответственно. В группе циклоспорина на 7-й день более 75 % поражения легочной ткани, по данным компьютерной томографии, было у 26 % пациентов против 52 % в группе сравнения, $p = 0{,}014$, потребность в респираторной поддержке (37 % против 63,6 %, $p = 0{,}011$); сатурация 88 (82–93 %) против 80 (70–86 %), $p = 0{,}001$ соответственно. Необходимость в респираторной поддержке на 11-й день после применения ИИЛ-6 повышала вероятность летального исхода (ОР 7,12 [2,51–20,10], $p = 0{,}001$). Факторы риска летального исхода: возраст старше 57,5 года, индекс массы тела более 30 кг/м^2, сатурация ниже 85,5 % в день применения ИИЛ-6. Длительность госпитализации составила 18,5 (14–24) дня против 18 (12–24) дней, $p = 0{,}778$. **ВЫВОДЫ:** Циклоспорин А в дополнение к ГКС и ИИЛ-6 для терапии COVID-19 может способствовать снижению летальности, частоты поступления в ОРИТ и потребности в респираторной поддержке.

КЛЮЧЕВЫЕ СЛОВА: циклоспорин А, COVID-19, SARS-CoV-2, летальность, респираторная поддержка

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Introduction

As of September 27, 2021 (at the end of study enrollment), the COronaVIrus Disease 2019 (COVID-19) pandemic has affected more than 200 countries, with 231,703,120 confirmed cases and 4,746,620 deaths worldwide [1]. Multicenter cohort studies and randomized trials as well as meta-analyses have shown a reduction in mortality with the use of glucocorticosteroids (GCS) and interleukin-6 receptor inhibitors (IL-6) in the devel-

opment of acute hypoxemic respiratory failure (ARF) in patients with COVID-19 [2–7]. These drugs are included in the Temporary Guidelines of the Ministry of Health of the Russian Federation "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" [8] as pathogenetic therapy for the development of systemic inflammation and lung damage. However, therapy for patients whose lung damage progresses despite the administration of GCS and IL-6 has not yet been developed.

Cyclosporine A is an immunosuppressive agent that suppresses the development of cell-type reactions: at the cellular level it blocks resting lymphocytes in the G0 or G1 phases of the cell cycle and suppresses antigen-triggered production and secretion of cytokines (including interleukin-2, T-lymphocyte growth factor) by activated T-lymphocytes , as well as T-lymphocyte-dependent antibody formation; in dendritic cells it modulates the expression of surface molecules that interact with T cells and the secretion of cytokines; in macrophages and neutrophils cyclosporine A reduces the production of cytokines that may play a protective role against pathogens [9]. Cyclosporine is a unique immunosuppressor because it blocks the transcription factor (NF-κB) through inhibition of calcineurin, which may interfere with the initial stage of development of the "cytokine storm" in severe COVID-19 [9, 10]. Cyclosporine A also disrupts the replication of ribonucleic acid (RNA) of the Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) virus and protein synthesis of viral particles. It is important that, unlike cytostatics, cyclosporine A does not suppress hematopoesis and does not affect the functioning of phagocytic cells. Many side effects associated with the use of cyclosporine are dose-dependent and reversible with dose reduction [11, 12].

The main targets of cyclosporine A in patients with COVID-19 are anti-inflammatory effect (inhibition of T-lymphocytes and reduction in the production of pro-inflammatory cytokines), antiviral effect (prevention of viral RNA synthesis), and action against angiotensin II. A number of researchers at the beginning of the pandemic proposed cyclosporine as a potential therapeutic drug for COVID-19 [13–15]. Data on the effectiveness of cyclosporine A are conflicting. Several clinical studies of cyclosporine in patients with COVID-19 report lower rates of death and suggest that this strategy should be studied further to assess in what context the benefit/risk profile of administering cyclosporine as first-line treatment for COVID-19 is most favourable [16–19]. There is limited data on the effective and safe use of cyclosporine A in the treatment of refractory multisystem inflammatory syndrome in children with COVID-19 [14]. Contrasting data were obtained in patients with rheumatic diseases, where mortality associated with COVID-19 was higher with the use of antirheumatic drugs, including cyclosporine A [20].

Purpose of the study

Evaluation of the effectiveness of cyclosporine A in patients with COVID-19 and hypoxemic ARF with progression of lung damage and lack of effect from therapy with GCS and IL-6 inhibitors.

Materials and methods

It was a retrospective pseudo-randomized single-center study of the effectiveness of cyclosporine A in hospitalized patients with COVID-19 and progressive hypoxemic ARF after the use of IL-6 inhibitors (tocilizumab or olokizumab) and glucocorticosteroids. The study included patients hospitalized from July 2020 to June 2021 at the University Clinical Hospital No. 4 of Sechenov University, repurposed for the treatment of COVID-19 (Moscow, Russia). The criteria for immunosuppressive therapy (tocilizumab or olokizumab in combination with glucocorticosteroids) were radiological findings compatible with SARS-CoV-2-associated pneumonia in combination with two or more of the following:

- reduction in hemoglobin oxygen saturation by pulse oximeter (SpO_2) ≤ 92%;
- C-reactive protein (CRP) > 60 mg/l or a 3-fold increase in CRP levels on days 8–14 of the disease;
- fever >38 °C for > 5 days;
- leukocyte count < 3000/μl;
- absolute lymphocyte count < 1000/μl;
- blood ferritin level > 500 ng/ml;
- IL-6 level > 40 pg/ml.

Inclusion criteria for the study were at least one sign of respiratory failure progression within 72 hours after administration of tocilizumab or olokizumab from the list below: decrease in SpO_2 from that measured on the day of tocilizumab or olokizumab administration (assessed 5 minutes after interruption of oxygen insufflation), increase in oxygen flow, need the use of non-invasive ventilation Constant Positive Airway Pressure (CPAP), progression of the area of lung damage on a computed tomogram (CT). Exclusion criteria were: the need for immediate endotracheal intubation, unstable hemodynamics (need for catecholamine administration and/or life-threatening arrhythmias), decompensation of chronic incurable diseases, immunosuppressive therapy for another disease at the time of COVID-19 onset, chronic hemodialysis, acute renal failure, acute myocardial infarction, acute cerebrovascular accident, pulmonary embolism, r any surgical intervention, age over 80 years, pregnancy.

The primary endpoint was in-hospital mortality. Secondary endpoints included total length of hospital stay, number of patients admitted to the intensive care unit (ICU), and proportion of patients requiring invasive or non-invasive ventilation.

Patients were retrospectively pseudorandomized into two groups: in the main group (Cyclosporine A group) patients received cyclosporine A (Sandimmun Neoral, Novartis) at a dose of 100 mg every 12 hours orally; in the comparison group (Control group) patients did not receive cyclosporine A therapy. We manually selected a cohort for the control group, which would match the main clinical and demographic features of those patients who received cyclosporine A therapy (the main group).

The comparison group consisted of patients who met the inclusion criteria but did not receive treatment with cyclosporine A.Those patients matched to the main group by gender, age, body mass index, concomitant diseases, percentage of lung damage, severity state according to the National Early Warning Score (NEWS2), and severity of respiratory failure (oxygen flow, SpO_2 without oxygen and the presence of continuous positive airway pressure — CPAP at the time of inclusion in the study).

Cyclosporine A therapy begun 72–96 hours after the administration of tocilizumab or olokizumab if ARF worsened, the duration of therapy was 7 days (with the possibility of extension to 21 days in the most severe cases, according to the decision of the medical council).

Demographic data and the presence of concomitant diseases were recorded in patients included in the study. On days 3, 7, 11 from the administration of tocilizumab, clinical data were recorded (blood pressure and heart rate, body temperature, respiratory rate, hemoglobin oxygen saturation by pulse oximeter, NEWS2 scale), level of respiratory support (low-flow oxygen therapy, oxygen flow in liters per minute, CPAP non-invasively through a face mask, or invasive mechanical ventilation - mechanical ventilation) and laboratory results (leukocytes, lymphocytes, platelets, creatinine, bilirubin, lactate dehydrogenase — LDH, ferritin, C-reactive protein). In the cyclosporine A group, clinical and laboratory data were recorded daily for the first 7 days. On the 3rd and 11th days after the administration of tocilizumab or olokizumab, patients underwent a chest CT scan to assess the percentage of lung tissue damage. All patients received basic therapy according to current clinical guidelines, including enoxaparin sodium at an average dose of 1 mg/kg/day subcutaneously.

Low-flow oxygen therapy was administered through nasal cannulas at flows up to 8 L/min, or a non-reversible mask with a reservoir bag at oxygen flows between 8 and 15 L/min. Non-invasive ventilation in CPAP mode was performed using Prisma 20C (Lowenstein, Germany), Prisma Vent 40 (Lowenstein, Germany), and RESmart GII Y30T (BMC, China) devices.

Statistical analysis

Statistical analysis performed using SPSS (version 23, IBM, USA). Data are presented as absolute values (frequencies) or medians (25th–75th percentiles) depending on the type and distribution of the data. Analysis of differences between groups was performed using the Mann—Whitney *U*-test, Chi-square test (χ^2) with Yates correction (Fisher's exact test for for 2 × 2 tables). Within group differences over time were evaluated using the Wilcoxon test.

Kaplan—Meier survival analysis was used for factors associated with mortality. Odds ratios (OR) were calculated. We used the Cox proportional model to determine hazard ratio [HR] with calculation of 95% confidence intervals (95% CI). We performed ROC analysis for risk factors of unfavourable outcome. Differences were considered statistically significant at $p < 0.05$.

This study conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association. Each patient provided written informed consent for participation in the study. The study protocol approved by the Local Ethics Committee of Sechenov University on April 27, 2023 (Protocol No. 07-23).

Results

The main study group included 54 patients, and 44 patients were selected from a cohort of 283 patients meeting the inclusion criteria into the comparison group. Patients were admitted to the hospital on Days 3–16 from the onset of the disease. In 80 (82%) patients, the volume of lung lesions according to computed tomography was no more than 50% at the time of admission. 93% of the patients had confirmed SARS-CoV-2 infection by polymerase chain reaction. Many patients had concomitant diseases — coronary heart disease, arterial hypertension, diabetes mellitus, obesity, etc. The main clinical and demographic characteristics of the patients are presented in Table 1.

Computed tomography data over time are presented in Table 2. As can be seen, the CT score in both groups progressively worsened.

Clinical indicators of the patients' condition are presented in Table 3.

Laboratory parameters of patients are presented in Table 4.

Survival was significantly higher in the cyclosporine group than in the control group, log-rank test $p = 0.004$, relative risk (RR) 5.55 (95% CI 2.29–13.44).

Patients in the cyclosporine group were found to have a 67% likelihood of earlier recovery than patients in the control group (Cox proportional model, RR 2.00 [1.12–3.48], $p = 0.018$), Figure 1.

Age and BMI reduced the probability of survival regardless of the therapy performed (RR 1.04 [0.99–1.09], $p = 0.056$, and RR 1.10 [1.05–1.15], $p = 0.001$, respectively).

Although the groups initially differed by the presence of arterial hypertension, Cox proportional model did not found significant effect of arterial hypertension on the outcome (HR 1.45 [0.17–2.96], $p = 0.303$).

Table 1. The demographic characteristics of patients (n = 98)

Parameter	Cyclosporine A, n = 54	Comparison, n = 44	p between groups
Age, years	57 (46–65)	60 (48–65)	0.333
BMI > 28 kg/m², n (%)	34 (63)	35 (79.5)	0.118
Men, n (%)	37 (68.5)	26 (59)	0.399
IHD, n (%)	23 (42.6)	24 (54.5)	0.310
AH, n (%)	25 (46.3)	30 (68)	0.050
CKD, n (%)	1 (1.9)	3 (6.8)	0.323
Diabetes meitus, n (%)	10 (18.5)	10 (22.7)	0.624
Lung disease, n (%)	7 (13)	3 (6.8)	0.504
Myocardial infarction or stroke in the anamnesis, n (%)	6 (11)	5 (11.4)	1.000
History of cancer, n (%)	3 (5.5)	1 (2.3)	0.625

Data are presented as absolute values (percentages), or medians (25th–75th percentiles). The p value between groups was calculated by the Mann—Whitney method or χ^2 and Fisher's exact test depending on the type of data.
AH — arterial hypertension; BMI — body mass index; CKD — chronic kidney disease; IHD — coronary artery disease.

The need for CPAP on Day 11 after IL-6 treatment increased the risk of death sevenfold (RR 7.10 [2.5–20.0], p = 0.001).

Respiratory rate on Day 7 after cyclosporine more than 22/min increased the probability of death (RR 1.38 [1.17–1.61], p = 0.001).

ROC analysis for mortality risk factors in all patients revealed the following (Figure 2, 3):

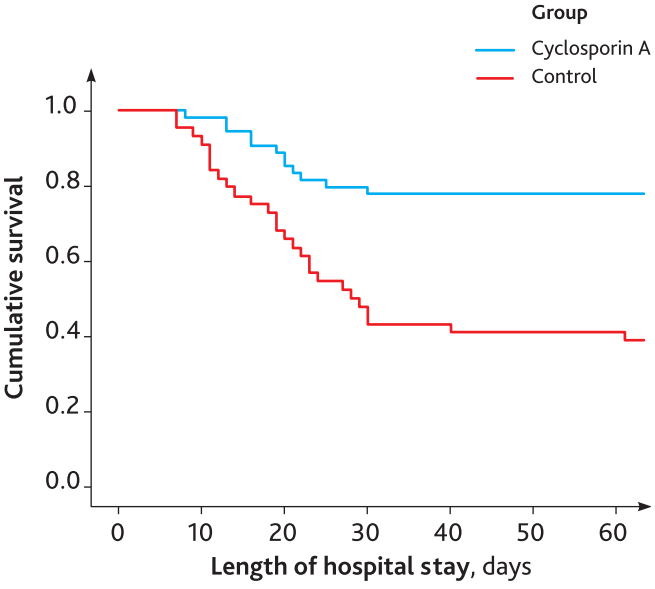

Fig. 1. Cumulative survival in Cyclosporin A and Control groups (HR 2.00 [1.12–3.48], p = 0.018 [Cox model])

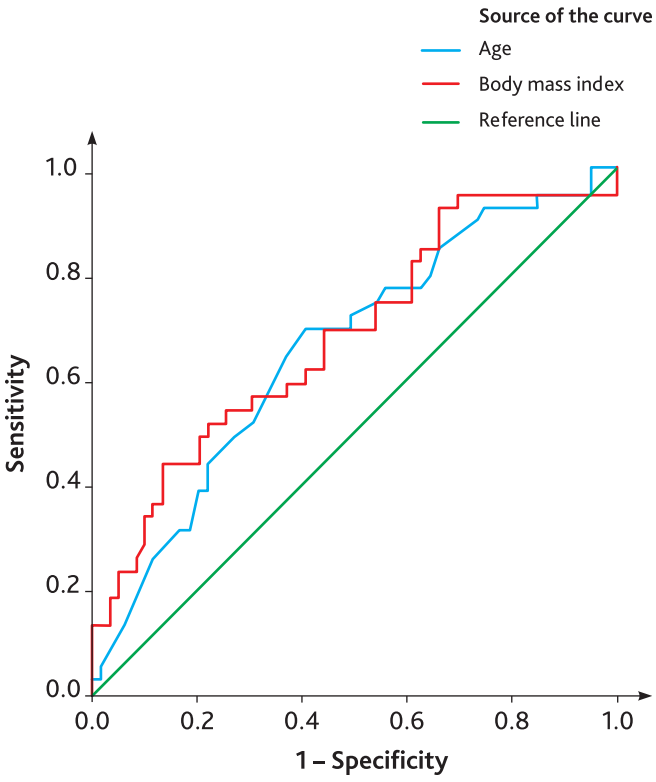

Fig. 2. ROC curves for mortality prediction for patients of both groups

Age — area under the receiver operator curve (AUROC) 0.65 (95 % CI 0.54–0.76), p = 0.011, cut-off value 57.5 years, sensitivity 74 %, specificity 60 %. Body Mass Index (BMI) — AUROC 0.68 (95 % CI 0.57–0.79), p = 0.003, cut-off value 30 kg/m², sensitivity 68 %, specificity 58 %.

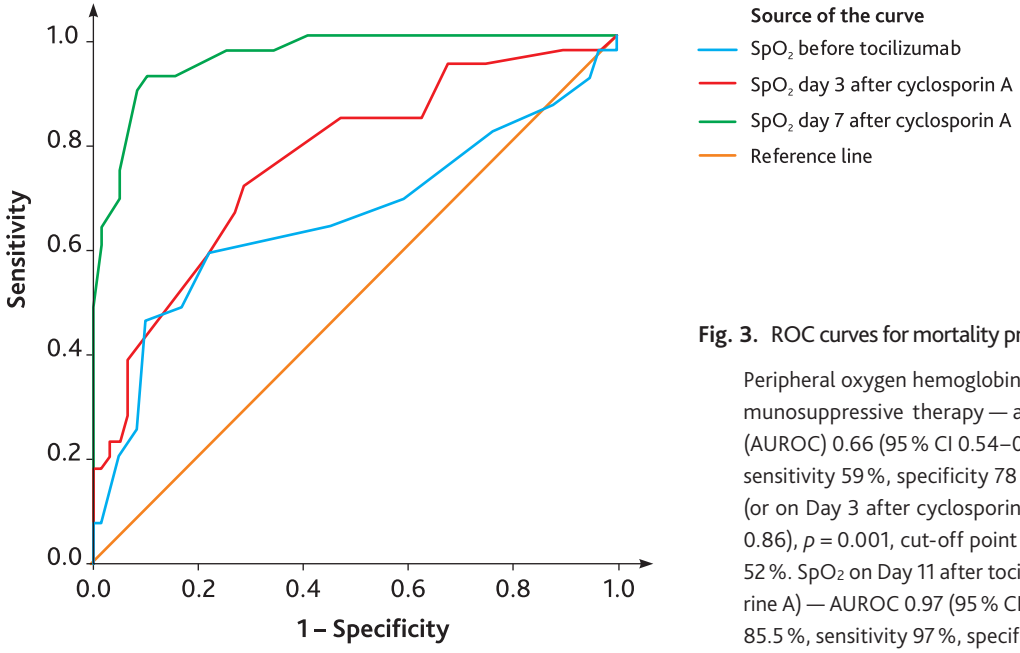

Fig. 3. ROC curves for mortality prediction for patients of both groups

Peripheral oxygen hemoglobin saturation (SpO_2) before initial immunosuppressive therapy — area under receiver operator curve (AUROC) 0.66 (95 % CI 0.54–0.78), $p = 0.010$, cut-off value 87.5 %, sensitivity 59 %, specificity 78 %. SpO_2 on Day 7 after tocilizumab (or on Day 3 after cyclosporine A) — AUROC 0.76 (95 % CI 0.67–0.86), $p = 0.001$, cut-off point 85.5 %, sensitivity 85 %, specificity 52 %. SpO_2 on Day 11 after tocilizumab (or on Day 7 after cyclosporine A) — AUROC 0.97 (95 % CI 0.93–0.99), $p = 0.001$, cut-off point 85.5 %, sensitivity 97 %, specificity 75 %.

Table 2. Computed tomography data in dynamics

Parameter	Cyclosporine A, *n* = 54	Comparison, *n* = 44	*p* between groups
On admission			
CT-1	13 (24)	4 (9)	0.169
CT-2	29 (53.7)	29 (66)	
CT-3	12 (22.2)	10 (22.7)	
CT-4	0	1 (2.3)	
CT grade	2 (1.75–2.00)	2 (2.00–2.75)	
At day 3 after IIL-6			
CT-1	1 (1.9)	0	0.084
CT-2	17 (31.5)	16 (36)	
CT-3	24 (44.4)	19 (43)	
CT-4	12 (22.2)	9 (20.5)	
CT grade	3 (2–3)	3 (3–3)	
*p within group	< 0.0001	< 0.0001	
At day 11 after IIL-6			
CT-1	8 (14.8)	2 (4.5)	**0.002**
CT-2	18 (33.3)	7 (16)	
CT-3	13 (24)	12 (27)	
CT-4	14 (26)	23 (52)	
CT grade	3 (2–4)	4 (3–4)	
*p within group	0.077	0.264	

* The difference within the group in dynamics from the previous evaluation was calculated by the Wilcoxon test.

Data are presented as absolute values (percentages) or medians (25^{th}–75^{th} percentiles). The p value between groups was calculated using χ^2 and Fisher's exact tests.

CT — computed tomography; CT-1 — up to 25 % lung involvement; CT-2 — 25–50 % lung involvement; CT-3 — 50–75 % lung involvement; CT-4 — more than 75 % lung involvement; IIL-6 — interleukin-6 inhibitors.

Table 3. Clinical characteristics of patients

Parameter	Cyclosporine A, *n* = 54	Comparison, *n* = 44	*p* between groups
Time from the onset of the disease to the administration of IL-6, days	9 (7–11)	9 (7–10)	0.501
Time from the onset of the disease to the administration of cyclosporine, days	13 (11–15)	—	—
Time from hospital admission to administration of IL-6, days	1 (1–2)	1 (1–2)	0.501
Time from hospital admission to administration of cyclosporine, days	5,5 (3–9)	—	—
Hospital length of stay, days	18,5 (14–24)	18 (12–24)	0.778
NEWS2 upon admission, points	**7 (6–8)**	**6 (4–7)**	**0.007**
NEWS2 on Day 3 after IIL-6, points	8 (7–8) $p = 0.012^*$	8 (6–8) $p = 0.001^*$	0.076
NEWS2 on Day 7 after IIL-6, points	7 (7–8) $p = 0.013^*$	7 (7–8)	0.076
NEWS2 on Day 11 after IIL-6, points	**6 (4.5–7.0) p = 0.001***	**7 (7–8)**	**0.030**
BP before IIL-6, mmHg	93 (83–110)	92 (81–109)	0.778
BP on Day 3 after IIL-6, mmHg	91 (82–110)	93 (83–110)	0.933
BP on Day 7 after IIL-6, mmHg	92 (83–112)	92 (81–113)	0.778
BP on Day 11 after IIL-6, mmHg	**90 (79–109)**	**83 (70–96)**	**0.020**
HR before IIL-6, min^{-1}	90 (80–94)	89 (79–95)	0.933
HR on Day 3 after IIL-6, min^{-1}	84 (76–92) $p = 0.012^*$	83 (72–93)	0.778
HR on Day 7 after IIL-6, min^{-1}	79 (74–85) $p = 0.019^*$	80 (74–90) $p = 0.001^*$	0.437
HR on Day 11 after IIL-6, min^{-1}	78 (73–86) $p = 0.901^*$	80 (73–90) $p = 0.001^*$	0.276
RR before IIL-6, min^{-1}	24 (23–25)	24 (22–25)	0.933
RR on Day 3 after IIL-6, min^{-1}	24 (22–26) $p = 0.685^*$	25 (24–27)	0.933
RR on Day 7 after IIL-6, min^{-1}	24 (23–25) $p = 0.634^*$	24 (23–25) $p = 0.001^*$	0.217
RR on Day 11 after IIL-6, min^{-1}	**22 (19.5–24.0) p = 0.001***	**24 (22–26)**	**0.001**
Body temperature before IIL-6, °C	38.0 (37.0–38.5)	37.8 (37.0–38.4)	0.149
Body temperature on Day 3 after IIL-6, °C	36.8 (36.6–38.1) $p = 0.001^*$	36.6 (36.1–36.8)	0.918
Body temperature on Day 7 after IIL-6, °C	36.8 (36.6–38.1) $p = 0.001^*$	36.6 (36.1–36.8)	0.918
Body temperature on Day 11 after IIL-6, °C	36.6 (36.6–36.6) $p = 0.001^*$	36.6 (36.5–36.8)	0.489
CPAP before IIL-6, *n* (%)	4 (7.4)	6 (13.6)	0.337
CPAP on Day 3 after IIL-6, *n* (%)	25 (46.3)	21 (47.7)	0.687
CPAP on Day 7 after IIL-6, *n* (%)	32 (59.3)	25 (56.8)	0.839
CPAP on Day 11 after IIL-6, *n* (%)	**20 (37)**	**28 (63.6)**	**0.011**
SpO_2 on room air before IIL-6, %	88 (87–91)	88 (85–91)	0.581
SpO_2 on room air on Day 3 after IIL-6, %	86 (83–88) $p = 0.001^*$	87 (86–89)	0.114
SpO_2 on room air on Day 7 after IIL-6, %	85 (80–86) $p = 0.088^*$	82 (80–87) $p = 0.580$	0.117
SpO_2 on room air on Day 11 after IIL-6, %	**88 (82–92,5) p = 0.029***	**80 (70–86) p = 0.001***	**0.001**
Oxygen flow on Day 3 after IIL-6, l/min	10 (7–15)	11 (9–14)	0.191
Oxygen flow on Day 7 after IIL-6, l/min	10 (8–15) $p = 0.189^*$	12 (9–16)	0.049
Oxygen flow on Day 11 after IIL-6, l/min	**8 (3–12,5) p = 0.004***	**15 (10–20) p = 0.030***	**0.001**

End of table 3

Parameter	Cyclosporine A, *n* = 54	Comparison, *n* = 44	*p* between groups
ICU admission, *n* (%)	14 (26)	29 (66)	0.001
Tracheal intubation, *n* (%)	14 (26)	29 (66)	0.001
Catecholamines, *n* (%)	12 (22)	27 (61)	0.001
Mortality, *n* (%)	12 (22)	27 (61)	0.001
Mortality in patients with BMI > 28 kg/m², *n* (%)	11 (32)	21 (60)	0.030

* The difference within the group in dynamics from the previous evaluation was calculated by the Wilcoxon test.

Data are presented as absolute values (percentages), medians (25^{th}–75^{th} percentiles). The p value between groups was calculated by the Mann—Whitney test or χ^2 and Fisher's exact test, depending on the type of data.

BMI — body mass index; CT — computed tomography; HR — heart rate; IIL-6 — interleukin-6 inhibitors (tocilizumab or olokizumab); MAP — mean arterial pressure; NEWS2 (National Early Warning Score) — early response scale; RR — respiratory rate; SpO_2 — oxygen saturation of hemoglobin by pulse oximetry.

- age —the area under receiver operator curve (AUROC) 0,65 (95% CI 0.54–0.76), $p = 0.011$, cut-off value 57.5 years, sensitivity 74%, specificity 60%;
- BMI — AUROC 0,68 (95% CI 0.57–0.79), $p = 0.003$, cut-off value 30 kg/m², sensitivity 68%, specificity 58%;
- SpO_2 before IIL-6: AUROC 0.66 (95% CI 0.54–0.78), $p = 0.010$, cut-off value 87.5%, sensitivity 59%, specificity 78%;
- SpO_2 on Day 7 after IIL-6 — AUROC 0.76 (95% CI 0.67–0.86), $p = 0.001$, cut-off value 85.5%, sensitivity 85%, specificity 52%;
- SpO_2 on Day 11 after IIL-6 — AUROC 0.97 (95% CI 0.93–0.99), $p = 0.001$, cut-off value — 85.5%, sensitivity — 97%, specificity — 75%.

Platelets were significantly higher and creatinine lower in the cyclosporine A group by the Day 11 after IIL-6 administration. There were no significant differences in bilirubin levels between groups. The incidence of nosocomial infections (pneumonia and urinary tract infections) in the cyclosporine group and in the control group was 13 (24%) *vs* 12 (27%), $p = 0.367$. The incidence of thrombotic complications in the cyclosporine group and in the control group was 7 (13%) *vs* 5 (11%), $p = 0.899$.

Discussion

The main finding of our study was a reduction in mortality, the need for the ICU admission, and decrease needs in respiratory and catecholamine support in patients who received cyclosporine A in addition to IIL-6 and glucocorticosteroids at a dose of 200 mg per day for 7 days. Patients in the cyclosporine group were 67% more likely to recover earlier than those in the comparison group (HR 2.0 [1.12–3.48], $p = 0.018$). Although data on the use of cyclosporine in COVID-19 are limited and mostly consists of observational studies, our data are in line with several studies. One of them, the first retrospective observational study involving 607 patients on the beneficial effect of cyclosporine in patients with severe COVID-19, demonstrated that the mortality rate in the cyclosporine group was significantly lower than in comparison group (14.23% *vs* 29.66%, respectively) [21]. According to our data, mortality in patients received cyclosporine A was also lower than in the comparison group (22% *vs* 61%, respectively). In a study by Guisado-Vasco P. et al. the time from the onset of symptoms to the start of treatment with cyclosporine was 11 days that is similar to our study (about 13 days). In abovementioned study age, the need for respiratory support, leukocytosis, lymphopenia, high levels of ferritin, CRP, history of hypertension, diabetes mellitus, lung diseases, and arterial thrombosis were risk factors for mortality [21]. We obtained a number of risk factors of death similar to the study by Guisado-Vasco P. et al.: leukocytosis, lymphopenia, high levels of ferritin and CRP, as well as thrombocytopenia. Additionally, in our study risk factors for mortality (determined using the Cox model) were age over 57.5 years, need for respiratory support (CPAP) on Day 7 after cyclosporine (Day 11 after IIL-6), BMI above 30 kg/m², oxygen saturation by pulse oximetry below 85.5%, respiratory rate on Day 7 after cyclosporine more than 22 per minute.

In a recent meta-analysis results from 145 included studies found that elevated plasma cytokine levels in patients with confirmed COVID-19 were associated with increased severity and mortality. In contrast, mild COVID-19 patients and survivors demonstrated functional innate and adaptive immune responses manifested by higher levels of eosinophils, lymphocytes, monocytes, B cells, natural killer cells, T cells, and it's CD4+ and CD8+ subsets. An increase in all of the above factors corresponded to an unfavourable course of the disease [1].

Table 4. Laboratory characteristics of patients

Parameter	Cyclosporine A, *n* = 54	Comparison, *n* = 44	*p* between groups
WBC before IIL-6, 1000/μl	6.7 (4.7–10.0)	5.9 (4.2–8.6)	0.311
WBC on Day 3 after IIL-6, 1000/μl	9.1 (5.6–12.1)	8.2 (5.3–11.0)	0.349
WBC on Day 7 after IIL-6, 1000/μl	**10.4 (8.3–13.8) *p* = 0.004***	**8.5 (6.3–10.9) *p* = 0.001***	**0.005**
WBC on Day 11 after IIL-6, 1000/μl	10.4 (8.0–11.4) *p* = 0.001*	10.0 (6.6–12.8) *p* = 0.001*	0.140
Lymphocytes before IIL-6, 1000/μl	0.8 (0.68–1.02)	0.7 (0.58–1.0)	0.349
Lymphocytes on Day 3 after IIL-6, 1000/μl	0.9 (0.6–1.1)	0.73 (0.62–1.0)	0.189
Lymphocytes on Day 7 after IIL-6, 1000/μl	**1.0 (0.64–1.5) *p* = 0.388***	**0.78 (0.6–1.0) *p* = 0.202***	**0.044**
Lymphocytes on Day 11 after IIL-6, 1000/μl	1.1 (0.8–1.9) *p* = 0.001*	0.9 (0.5–1.3) *p* = 0.001*	0.081
Platelets before IIL-6, 1000/μl	182 (139–225) *p* = 0.001*	161 (132–219)	0.189
Platelets on Day 3 after IIL-6, 1000/μl	198 (145–265)	174 (135–205)	0.349
Platelets on Day 7 after IIL-6, 1000/μl	250 (170–322) *p* = 0.001*	219 (185–280) *p* = 0.001*	0.205
Platelets on Day 11 after IIL-6, 1000/μl	**255 (198–361) *p* = 0.008***	**209 (151–277) *p* = 0.022***	**0.029**
CRP before IIL-6, mg/l	64 (34–119)	73 (36–98)	0.932
CRP on Day 3 after IIL-6, mg/l	11,8 (2,9–48,5) *p* = 0.001*	14 (5–37)	0.816
CRP on Day 7 after IIL-6, mg/l	**2.9 (1.0–5.4) *p* = 0.001***	**10 (3–24) *p* = 0.001***	**0.001**
CRP on Day 11 after IIL-6, mg/l	**1.45 (0.72–2.7) *p* = 0.001***	**2.3 (1.25–5.6) *p* = 0.001***	**0.042**
LDH before IIL-6, IU/l	629 (499–842)	615 (498–850)	0.878
LDH on Day 3 after IIL-6, IU/l	770 (616–1002)	568 (476–665)	0.878
LDH on Day 7 after IIL-6, IU/l	**928 (720–1149) *p* = 0.170***	**748 (499–1004) *p* = 0.166***	**0.038**
LDH on Day 11 after IIL-6, IU/l	695 (537–914) *p* = 0.981*	898 (466–1275) *p* = 0.041*	0.411
Ferritin before IIL-6, μg/l	868 (414–1028)	587 (380–1493)	0.964
Ferritin on Day 3 after IIL-6, μg/l	828 (458–1226)	392 (295–919)	0.964
Ferritin on Day 7 after IIL-6, μg/l	948 (608–1080) *p* = 0.374*	829 (444–1453) *p* = 0.308*	0.832
Ferritin on Day 11 after IIL-6, μg/l	924 (641–1162) *p* = 0.248*	668 (481–966) *p* = 0.243*	0.172
Creatinine before IIL-6, μmol/l	85 (64–125)	84 (65–131)	0.878
Creatinine on Day 3 after IIL-6, μmol/l	87 (68–131)	88 (69–130)	0.932
Creatinine on Day 7 after IIL-6, μmol/l	87 (66–145)	93 (64–154)	0.067
Creatinine on Day 11 after IIL-6, μmol/l	84 (64–129) *p* = 0.877*	93 (77–152) *p* = 0.079*	0.028
Bilirubin before IIL-6, μmol/l	8.9 (6.6–13.1)	9.1 (6.7–13.0)	0.933
Bilirubin on Day 3 after IIL-6, μmol/l	9.1 (6.8–13.4)	9.1 (6.8–13.3)	0.933
Bilirubin on Day 7 after IIL-6, μmol/l	9.2 (7.4–14.5)	9.4 (7.3–14.6)	0.878
Bilirubin on Day 11 after IIL-6, μmol/l	9.3 (7.3–14.4) *p* = 0.174*	9.4 (7.5–14.8) *p* = 0.125*	0.878

* The difference within the group in dynamics from the previous evaluation was calculated by the Wilcoxon test.

Data are presented as median (25^{th}–75^{th} percentiles). *p* between groups was calculated by the Mann—Whitney test.
CRP — C-reactive protein, IIL-6 — interleukin-6 inhibitors (tocilizumab or olokizumab); **LDH** — lactate dehydrogenase, WBC — white blood cells.

LDH levels in our study increased with the course of the disease. The dynamics of LDH were interesting: in the cyclosporine group it increased and then decreased, but the differences did not reach statistical significance due to the wide scatter of data; in the comparison group, LDH increased over time, but at the only statistically significant point it was lower than in the cyclosporine group. In a retrospective study, Vélez-Páez J.L. et al. in 240 patients living at high altitudes (2850 m above sea level), LDH levels were similar to our data and showed a significant increase in deceased patients, but this indicator was insignificant as a predictor of an unfavorable course of the disease [22]. Another retrospective study of 450 patients identified BMI, LDH, CRP, and albumin as continuous variables associated with lesion grade on chest CT. Cox proportional hazards analysis identified LDH (HR 1.003; 95 % CI 1.001–1.005) as a factor independently associated with the development of severe COVID-19 pneumonia. Elevated serum LDH levels on admission may be useful in clinical practice to easily screen COVID-19 patients at high risk of developing subsequent severe disease (risk increased exponentially by 2, 3, 6, 10, and 18 times as LDH increased by 200, 400, 600, 800 and 1000 above upper limit of the reference range) [23].

On the contrary, arterial hypertension was not confirmed as a risk factor in any group or in the entire cohort of patients. The NEWS2 scale has once again demonstrated its validity. Patients in both groups showed tachycardia and tachypnea at the beginning of treatment that decreased significantly on Day 7 after tocilizumab administration. According to CT data, there were significantly fewer patients with CT-4 (26 % *vs* 52 %, $p = 0.014$), the need for oxygen therapy (10 [9–16] L/min *vs* 12 [10–17] L/min, $p = 0.049$, respectively), and CPAP dependency (37 % *vs* 63.6 %, $p = 0.011$, respectively) in the cyclosporine group on Day 11 from the use of tocilizumab.

A number of data may indirectly support the potential therapeutic effect of cyclosporine A in SARS-CoV-2 infection. Some studies have reported a low incidence of COVID-19 among individuals with rheumatic diseases [24, 25] or a better prognosis in kidney transplant recipients [26]. Cyclosporine A-based immunosuppressive treatment may be safe and effective for kidney transplant recipients diagnosed with COVID-19 [26]. Patients with solid tumors, human immunodeficiency virus, and primary immunodeficiencies are at high risk of severity progression, tracheal intubation, or death. Data from patients receiving immunosuppressants or gene-modified biologic therapy to treat connective tissue and autoimmune diseases showed clinical outcomes similar to those in the general population. In other studies the use of rituximab and specific immunosuppressive drugs (eg, sulfosalazine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate, or tacrolimus) were associated with worse outcomes compared with the use of methotrexate or disease-modifying antirheumatic drugs [27].

Many researchers have described an increase in IL-6 levels in patients with COVID-19 [26]. But IL-6 is not the only marker of inflammation in COVID-19. Other inflammatory parameters have shown associations with mortality or severe disease, such as D-dimer > 2.5 μg/mL or CRP levels greater than 100–200 mg/L and their combination [28–30]. We did not measure IL-6 and D-dimer levels in all of our patients due to financial constraints. However, some studies have shown conflicting data on the prognostic significance of IL-6 in COVID-19 [31].

In a small study ten moderately ill patients received cyclosporine at an initial dose of 9 mg/kg/day [32]. Five of them experienced side effects, none of which were serious, the most common being an increase in transaminases. None of the participants in this study required intensive care, and all were discharged from the hospital [32].

In a pilot study of 209 patients with moderate-to-severe COVID-19, cyclosporine was administered orally at a dose of 1–2 mg/kg/day for 7 days from hospital admission as an adjuvant to steroid therapy [33]. Patients with admission creatinine values > 2 mg/dL or uncontrolled hypertension were excluded. In this study, cyclosporine use was associated with mortality reduction [33]. Low doses and short-term regimen in the study by Gálvez-Romero J.L. did not lead to the development of side effects in comparison with the nephrotoxicity observed in transplant patients with long-term use of cyclosporine [34, 35]. In our study we used low doses of the drug adjusted for weight and compatibility with other drugs for a short time to minimize the adverse side effects of cyclosporine.

According to various studies, the prevalence of superinfections in patients with COVID-19 is heterogeneous, with differences of more than 50 % depending on the site of infection, comorbidities and immunosuppressive drug use [36]. The incidence of nosocomial infections in our study was similar to comparator studies [37–40]. Diagnostic of nosocomial infection in our patients was a challenge due to difficulties to use traditional criteria for infection after immunosuppression therapy (temperature, leukocytosis and purulent sputum).

Five prospective randomized trials are currently planned and ongoing to evaluate the effectiveness of treatments for COVID-19, including cyclosporine. The largest of these is the I-SPY COVID-19 trial, a multicenter, multi-arm, adaptive, open-label, randomized controlled phase II trial for 11 treatment regimens including cyclosporine 5 mg/kg/day for 5 days in combination with remdesevir and dexamethasone [40]. Another phase II trial planned to include 75 non-ICU inpatients that will be randomized 2 : 1 to cyclosporine A (2.5 mg/kg orally twice daily, 7 days) plus standard care or standard care only [43]. Another phase IV study will be an open-label, controlled, randomized clinical trial to evaluate the efficacy and safety of standard treatment plus cyclosporine as compared to standard treatment in inpatients with COVID-19 infection to assess patient's clinical features over 12 days of treatment [44]. The next study will include 150 COVID-19 patients with ARF and use cyclosporine of 6 mg/kg/day orally divided by two doses for 8–14 days in patients with normal renal function [45]. The latest registered retrospective study planning to include 100,000 patients, "Clinical characteristics and prognostic factors of patients

with COVID-19 using big data and artificial intelligence methods (BigCoviData)", which, in addition to demographic, clinical, laboratory and instrumental data, will analyze the types and characteristics treatment regimens. Data collection is scheduled to be completed in 2023 [46].

Study limitations

The major limitations of our study were its observational and retrospective nature, relatively small sample size, lack of viral load data, and short follow-up period. We studied only a few specific inflammatory and hematological markers; D-dimer and advanced coagulation parameters were not available. We did not conduct a comparative analysis of the effectiveness of therapy in patients who received tocilizumab or olokizumab. We did not study different strains of COVID-19 which might have influenced the results although the cohort was studied over a relatively short period of time corresponding to the early peaks of the pandemic when delta, beta and alpha strains of SARS-CoV-2 predominated.

Conclusion

Thus, in patients with COVID-19, the use of cyclosporine A in addition to tocilizumab and glucocorticosteroids may reduce mortality, the need for ICU admission, and may also prevent the need for escalation of respiratory support. Randomized controlled trials are urgently needed to confirm or refute these results.

Disclosure. The authors declare that they have no competing interests.

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