Original Article

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Improved Clinical Outcome with Cyclosporine in Patients with Moderate to Severe COVID-19 Infection

Aysha Ghayyur[1], Farah Shafi[2], Saman Shahid[3], Bushra Azam[4], Sana Fatima[5], Syed Shahzad Hussain[6], Nabil[1]

[1,7]Department of Medicine, Allama Iqbal Medical College, Jinnah Hospital, Lahore
[2,4,5]Department of Medicine, Ameer ud din Medical College, Lahore
[3]Department of Sciences & Humanities, National University of Computer & Emerging Sciences (NUCES), FAST Lahore, [6]Department of Neurosurgery, Punjab Institute of Neurosciences (PINS), Lahore

Author`s Contribution

[1]Study design, [2]methodology and paper writing, Data collection and calculations, [3]Analysis of data and interpretation of results, [4,5]Literature review and referencing, [6,7]Editing and quality insurer.

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Address of Correspondent
Prof. Dr. Saman Shahid
Department of Sciences & Humanities, National University of Computer & Emerging Sciences, Lahore
drshahidsaman@gmail.com

ABSTRACT

Objective: To investigate the potential benefits of adding cyclosporine to the presently recommended conventional treatment for COVID-19 disease.

Methodology: A retrospective cross-sectional research was carried out on COVID-19 patients with moderate-to-severe severity who were admitted to Lahore General Hospital's ICU (intensive care unit) or HDU (high dependency care unit from 2020 to 2021. Patients aged 18 to 70 with moderate to severe illness were included, while those with specific conditions were excluded. Data on symptoms, oxygen saturation levels, and medication usage were collected and analyzed using statistical tests. The assessment of outcome decreased dependence on oxygen in ICU/HDU was assessed through a combination of different drugs (treatment), especially the inclusion of Cyclosporine, which was done with Chi-square and Binomial tests.

Results: In the study 46% are male and 54%are females. 71% of patients suffer fever while 69% observed shortness of breath out of which 44% had cough. On presentation 30.8% were mild cases (out of which27% converted to moderate on second day), 17.3% fall in moderate cases while 51.9% are severe COVID cases while on treatment day 7 results shows 30.6% patients are oxygen free, 10% cases are moderate cases while 19% were severe cases.53.8% remain alive while deaths are 46.2% which is a good number in ICU/HDU cases.

Conclusion: Cyclosporine use should be considered in SARS-CoV-2 moderate and severe disease because it not only improves the disease severity, reduces oxygen demand and improves mortality.

Keywords: Calcineurin Inhibitor Cyclosporine, COVID-19 infection, Shortness of Breath, Oxygen Saturation.

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Introduction

Cyclosporine is reported to enhance the clinical outcome of COVID-19 patients with moderate to severe disease. The COVID-19 infection is an immediate global health risk which manifests long-term consequences as well both physical and psychological. Previous research has demonstrated that six coronaviruses may cause disease in humans; however, four of them are thought to be low pathogenic coronaviruses that cause moderate upper respiratory tract infections, as opposed to the highly pathogenic β-coronaviruses. Both MERS (Middle East respiratory syndrome-related corona virus) and SARS-Cov-2 may result in deadly viral pneumonia and severe lower airway infections. There are 20.6 million infective cases out of which 351,690 people died. The complete effect of this virus on the body is not evident and this leads to the motivation that world is trying one after another drug to deal with it. There are many trials using Remdesvir, Lopinavir, Ritonavir, HCQ (Hydroxycloroquine), Janus kinase inhibitors (Baricitanib), Tocilizumab and many

more. But being a third-world country fighting the pandemic provision of all these fancy medications for all the underprivileged patients is still a challenge. This makes the doctors and the researchers keep on thinking about the less expensive and easily administrable options to defeat the viral mechanism.[1-6]

Cyclosporine A (calcineurin inhibitor) is a potent immunosuppressant that works by inhibiting B-cells and T-cells. It was discovered in the 1970s and works wonders in organ transplants. This drug not only decreases acute graft rejection but also increases early graft survival.[7] Cyclosporine has been used successfully in the treatment of multiple diseases of autoimmune origin like severe deforming Rheumatoid Arthritis, Psoriatic Arthritis, Systemic Lupus Erythematosus, Type-1 diabetes mellitus, inflammatory bowel diseases, Graves' disease, and myasthenia gravis. In dermatology, it is used as a primary therapy for Psoriasis, Pyoderma Gangrenosum, Behçet's disease, Atopic Dermatitis, Lichen Planus, etc., at a dose of 3 to 5 mg/kg per day, this dose increases up to 15mg/kg in transplant patients to prevent organ rejection.[8-11]

Cyclosporine has immunosuppressive properties, but it also has anti-inflammatory properties since it inhibits the synthesis of interleukin-2 (IL-2) by blocking the activation of nuclear factor of activated T cells (NF-AT). Because of its multiportal action in COVID-19, cyclosporine can assist to avoid the cytokine storm in cases of severe COVID-19. For example, SARS-COVID non-structural protein 1 also exhibits IL-2 production through NF-AT activation.[12] Cyclosporine binds to cyclophilin-D and prevents the mitochondrial membrane from opening.[11] Permeability transition pore, by this mechanism it prevents the cellular damage from oxidative stress injury and hypoxia. [13] It also shows antiviral properties as well at the micro level by blocking the COVID19 viral replication through cyclophilin D replication.[14] Therefore, in cases with severe COVID-19, cyclosporine may be a useful option for preventing the cytokine storm and deactivating viral replication. Hypertension and nephrotoxicity are the potent side effects of cyclosporine which should be monitored carefully and it should not be used in renal failure patients. Many clinical trials are using different doses of cyclosporine in COVID-19 infection. Furthermore, it is not an expensive drug that can be opted for worldwide. The goal of the current study is to ascertain whether adding drug Cyclosporine to the already accepted standard therapy for COVID-19 disease has any positive benefits.

Methodology

This retrospective cross-sectional research was carried out on COVID-19 patients with moderate-to-severe severity who were admitted to Lahore General Hospital's ICU (intensive care unit) or HDU (high dependency care unit).

Patients between the ages of 18 and 70 with COVID-19 infection and moderate to severe illness were included in the study. The study excluded cases of viral infections, any other serious condition that is a candidate for ICU, cases of active tuberculosis, patients with TLC of more than 15×10^9/L, cases of acute bacterial infection, and patients with renal failure.

Moderate-level COVID-19 severity includes the following points: (i) Presence of symptoms suggestive of COVID-19, (ii) Hypoxia (oxygen saturation <93% but >90%) at room air, (iii) X-ray chest with infiltrate involving <50% of the lung field, and (iv) No complication or manifestation related to severe disease. Whereas, the Severe COVID-19 Infection includes the following points: (i) Clinical features of pneumonia, (ii) Respiratory rate > 30 per minute, (iii) Oxygen saturation <90%, at room air, (iv) Chest X-ray with infiltrates involving > 50% of lung field, and (v) Patient in critical phase (like multi-organ dysfunction, ARDS, Septic Shock).[15]

Cyclosporin doses: 12 -14 mg/kg in two divided doses for five days a dose usually used to prevent graft rejection. The Remdesiver was administered 200 mg IV on day one and subsequently 100 mg IV daily on days two through five. Etanercept was administered 50 mg s/c (Inj.) once weekly, while Tocilizumab was administered 4–8 mg/kg once IV over 60 minutes. The Etanercept, Tocilizumab, and Remdesivir were used where the Cyclosporine was contraindicated or the patient was already taking any of these drugs.

The patients admitted to the High Dependency Unit (HDU) or Intensive Care Unit (ICU) were selected as per inclusion or exclusion criteria. The study conformed to the ethical review board requirements. Approval was taken from the ethical board of the hospital. Confidentiality and anonymity-related issues were ensured. The data was collected on a self-designed preform.

The data was collected through a pre-designed proforma. The data was then analyzed on SPSS Version 26. The Chi-Square Test for One Variance test (for more than one category) is used to compare the variance of a sample to a known population variance. The population variance and assumed that the sample was drawn from a normally

distributed population. We used this test to test a null hypothesis (no effect on the disease severity with the intake of Cyclosporine) with an alternative hypothesis (disease severity decreases as oxygen dependence is observed to decline). We also applied a one-sample binomial test (for two categories/single binary variables) to compare the two proportions. The assessment of outcome decreased dependence on oxygen in ICU/HDU was assessed through a combination of different drugs (treatment), especially the inclusion of Cyclosporine, which was done with Chi-square and Binomial tests. At a p-value of less than 0.050, we rejected the null hypothesis, and at a p-value greater than 0.050, we retained the null hypothesis.

Results

Patients between 18 years to 76 years were included in the study. There were 24(46%) male and 28(54%) female patients.

Table I presents details on the clinical signs and symptoms of the patients at presentation. 69% of patients were observed with dyspnea, cough was observed in 44%, and fever in 71% of patients. However, 63.5% of patients were not found with an altered state of consciousness. 75% of patients had blood pressure within in normal range (91-120/61-90). Around 52% of patients had a temperature of 100 ºF and 36.5% of patients' X-ray (CXR) findings suggested the severe COVID illness (air space opacities/infiltrates typically bilateral started from peripheries involving more than half of lungs), whereas, 44% patients had CXR involvement proposing moderate COVID.

Table II presents the details on oxygen-saturation levels at presentation, on the second day, and on the seventh day. At presentation, there were more patients (52%) with SpO2 levels < 90% (severe cases) as compared to mild cases (31%) or moderate cases of COVID-19 (17.3%). However, on the 2nd day, only 3.8% were maintaining oxygen saturation without any support, and the rest 96.2% were oxygen dependent, while on the 7th day of treatment, we can see almost 31% of patients were breathing in room air, 10% maintained oxygen saturation on 1-4 liters of oxygen. It is obvious that from 2nd day onwards, more patients (3.8%, then 15.4%, & then 31%), were breathing in room air. Overall, 53.8% of patients survived.

Table III describes details on patients who have mentioned drug(s). 75% were taking anti-coagulants, 98% were given steroids and antibiotics, and Colchicine and Ivermectin were taken by 60%. Around 60% of the patients were taking Cyclosporine and 40% either the cyclosporine was contraindicated or the patient was on some other immunosuppressant like Etanercept, Remdesivir, and Tocilizumab.

Table I: Clinical /Sign & Symptoms at presentation. (n=52)

Parameters	Sub-groups	N(%)
Dyspnea	Present	36(69.2%)
	Absent	16(30.8%)
Cough	Present	23(44.2%)
	Absent	29(55.8%)
Fever	Present	37(71.2%)
	Absent	15(28.8%)
Diarrhea	Present	4(7.7%)
	Absent	48(92.3%)
Vomiting	Present	7(13.5%)
	Absent	45(86.5%)
Altered state of consciousness (ASOC)	Present	19(36.5%)
	Absent	33(63.5%)
Limb weakness	Present	9(17.3%)
	Absent	43(82.7%)
Blood pressure <140/90 (normal as per JNC*)	< 90/60	6(11.5%)
	91-120/61-90	39(75%)
	>140/90	7(13.5%)
Pulse Normal: 60-90	60-90	19(36.5%)
	91-110	21(40.4%)
	>110	12(23.1%)
Temperature (ºF) Average body temperature: 98.6 ºF	98-100	25(48.1%)
	100	27(51.9%)
Chest X-ray (CXR)	<30% lung involvement (mild)	10(19.2%)
	30-50% lung involvement (moderate)	23(44.2%)
	>50 lung involvement (severe)	19(36.5%)

The graphical outputs of the one-sample binomial and chi-square tests are indicated in Figures 1-6. Figure 5 shows the oxygen saturation of the patients on Day 2 (next day after the presentation day). Here most of the patients fall in the column showing >90 % of oxygen on 5-10 liters of oxygen. The significant p-value (0.001) shows that we can reject the null hypothesis and retain the alternative hypothesis (disease severity decreases as oxygen dependence is observed to decline), according to which we can infer that our clinical management, especially the use of Cyclosporine was effective in maintaining a good outcome and that is why more than half (54%) were survived and discharged.

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Table II: Status of Oxygen-Saturation (SpO_2) at presentation, second day, third day, and on 7th day. (n=52)		
Parameters	Sub-groups	N(%)
SpO_2 @ presentation	>93 (mild)*	16(30.8%)
	90-93 (moderate)*	9(17.3%)
	< 90 (severe)*	27(51.9%)
SpO_2 @ day 2	90-93 (room air)	2(3.8%)
	>90 on 1-4 liters of oxygen	7(13.5%)
	>90 on 5-10 liters of oxygen	21(40.4%)
	>90 on 10-15 liters of oxygen	9(17.3%)
	<90 on 15 liters of oxygen	13(25%)
SpO_2 @ day 3	90-93 (room air)	8(15.4%)
	>90 on 1-4 liters of oxygen	10(19.2%)
	>90 on 5-10 liters of oxygen	9(17.3%)
	>90 on 10-15 liters of oxygen	9(17.3%)
	<90 on 15 liters of oxygen	14(26.9%)
	Expired	2(3.8%)
SpO_2 @ day 7	90-93 (room air)	16(30.8%)
	>90 on 1-4 liters of oxygen	5(9.6%)
	>90 on 5-10 liters of oxygen	5(9.6%)
	>90 on 10-15 liters of oxygen	8(15.4%)
	<90 on 15 liters of oxygen	10(19.2%)
	Expired	8(15.4%)
Respiratory rate /min (RR) Normal: 16-18	Up to 18	3(5.8%)
	19-22	30(57.7%)
	>23	19(36.5%)
Outcome	Discharge	28(53.8%)
	Deaths	24(46.2%)

Table III: Intake of Drugs (n=52)		
Parameters	Sub-groups	N(%)
Anti-coagulants	Not given	13(25%)
	Given	39(75%)
Steroids	Not given	1(1.9%)
	Given	51(98.1%)
Antibiotics	Not given	1(1.9%)
	Given	51(98.1%)
Etanercept	Not given	41(78.8%)
	Given	11(21.2%)
Ivermectin	Not given	21(40.4%)
	Given	31(59.6%)
Tocilizumab	Not given	46(88.5%)
	Given	6(11.5%)
Remdesivir	Not given	48(92.3%)
	Given	4(7.7%)
Colchicine	Not given	45(86.5%)
	Given	7(13.5%)
Cyclosporine	Not given	21(40.4%)
	Given	31(59.6%)

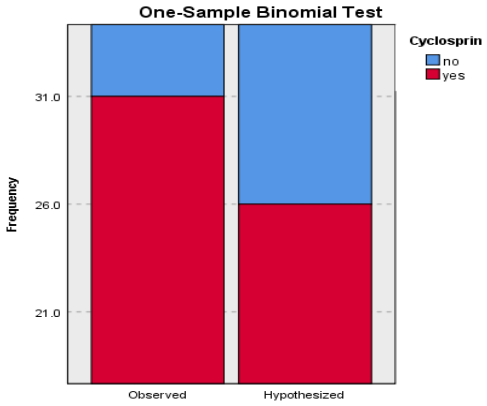

Figure 1. This graph shows the percentage of patients who received cyclosporine. (p-value: 0.212)

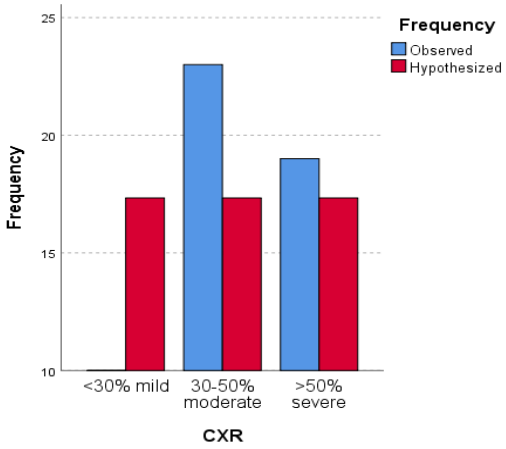

Figure 2. 30-50 percent of cases as moderate COVID and greater than 50 percent are severe COVID cases. (p-value: 0.077)

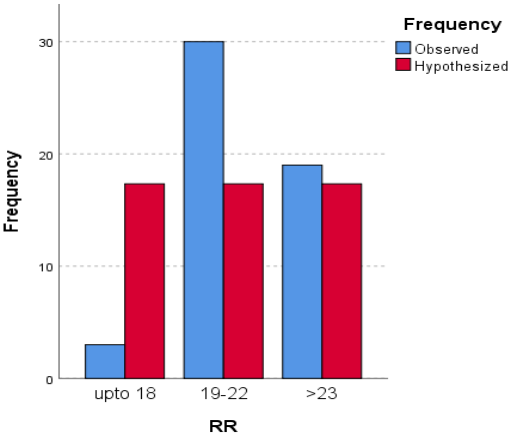

Figure 3. Respiratory rate (per min) at presentation. In this graph, as we can observe most of the patients are tachypneic with a respiratory rate of greater than 18 breaths/min at presentation to the hospital (p-value: 0.000)

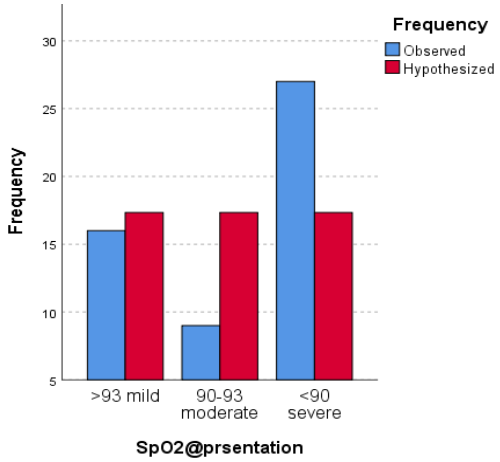

Figure 4. Here we observe the Oxygen saturation of patients on presentation to the hospital emergency. The red bar shows equal value for reference and the blue bar shows the results when most of the cases are in a severe category that they are unable to maintain oxygen saturation of less than 90 percent. (p-value: 0.009)

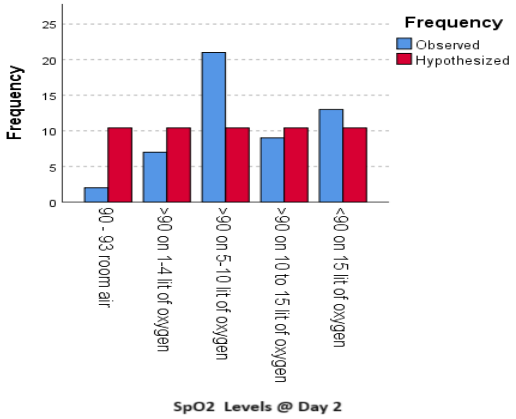

Figure 5. This graph shows the oxygen saturation of the patients on Day 2 (next day after the presentation day). Here most of the patients fall in the column showing >90 % of oxygen on 5-10 liters of oxygen. (p-value: 0.001; Rejected the null hypothesis)

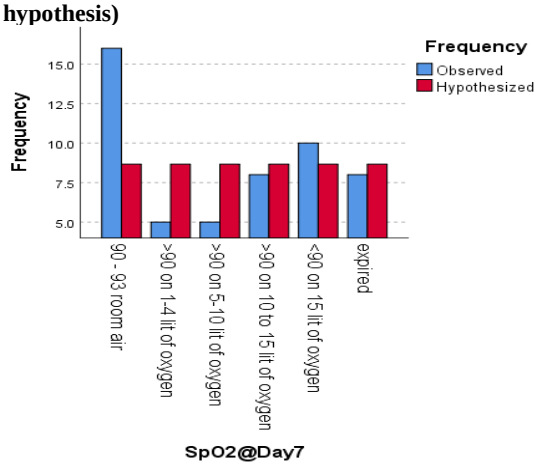

Figure 6. This shows the oxygen saturation of Day 7. Here we can see that the majority of patients are in column showing mild COVID which means patients can maintain oxygen saturation at room air. (p-value: 0.087)

Discussion

The outcome of our study speaks in favor of cyclosporine's use and efficacy in COVID-19, with more patients able to maintain oxygen saturation and able to survive over a few days. However, adding it to the presently recommended treatment for coronavirus still requires in-depth research and analysis from efficacy to adverse effects taking into consideration a more significant number of people and across various setups. The current study suggests that besides cyclosporine's conventional use as an immunosuppressant for post-transplant organ rejection [11], it can also greatly benefit COVID-19 patients. Another research by Poulsen et al. found that because transplant patients frequently have a high incidence of additional risk factors such as hypertension, diabetes, and obesity, calcineurin inhibitors may offer protection against severe illness and eventually mortality in the case of COVID-19.[16]

In comparison to other competitor drugs for coronavirus, such as Remdesivir-a mono-phosphoramidate prodrug of an adenosine analog with a broad-spectrum antiviral activity against coronavirus[17] and Tocilizumab, an antibody that blocks the IL-6 receptor [18], etc. it might not be entirely effective. Still, it is more cost-effective for a third-world country such as Pakistan. Various studies conducted across the globe reveal that the active immunophilin pathway plays a role in the replication and growth of the coronavirus, while cyclosporine functions by inhibiting this pathway.[14] A study suggests that cyclosporine at a nontoxic concentration can regress the growth of several types of coronavirus in vitro[19] ; however, its *in vivo* effects are yet to be confirmed. Another study implies that cyclosporine dosage in treating most patients is too low to eliminate the virus effectively. One challenge is attaining sufficient tissue concentration, as the main virus load does not exist in serum while it is in the lungs/airways, and cyclosporine concentration in the serum is higher than in the lungs. Moreover, the dosage required to effectively treat severe COVID-19 infections would be 3 to 6-fold higher, which would, in turn, result in severe adverse/toxic effects such as nephrotoxicity.[20] The only way to reach a practical level of local (airways/lungs) concentration would be through inhaled cyclosporine.[21] However, there is no human availability of in vivo evidence of an antiviral effect of Inhaled cyclosporine, so it cannot be advised as routine treatment.

Conclusion

Calinurin inhibitor cyclosporine has a proven effect on moderate to severe COVID-19 infection in terms of decreasing the oxygen demand and reducing disease severity shown by a smaller number of days of stay at the hospital and lesser mortality in critically sick patients. To conclude, cyclosporine use should be considered in SARS-CoV-2 induced impending cytokine storm where not many options are left.

Limitations: The shortcomings of our study lie in the fact of not taking into consideration the all-cause mortality, adverse events, and more or less the mechanical ventilation.
Recommendations: A large-level study with a greater number of patients from other parts of the world should be done to clarify the role of cyclosporine in COVID-19 infection.

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